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American Heart Journal

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Original Communications

THE CLINICAL SYNDROME ASSOCIATED WITH PULMONARY ARTERIOVENOUS FISTULAS, INCLUDING A CASE REPORT OF A SURGICAL CURE

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ROCHESTER, MINN.

WHEN a young person presents himself for medical examination with cyanosis, clubbing of the fingers and toes, and polycythemia, the most common etiological condition is congenital heart disease. That such a picture may be associated with an arteriovenous shunt in the lesser circulation has become of increased diagnostic importance, for, with the recent advances in the field of thoracic surgery, complete cure of the condition may be effected with minimal operative risk. The relationship between polycythemia and a pulmonary arteriovenous shunt was first clearly elucidated by Hepburn and Dauphinee,[1] in 1942, in a case in which the patient was cured by pneumonectomy.‡ The first case in which a clinical diagnosis was made was reported by Smith and Horton[2] in 1939. Previous to these first clinical studies, there had been anatomic descriptions of the pulmonary lesions following post-mortem examinations by Churton,[3] Wilkens,[4] and Rodes.[5] The case recorded by Churton contains few data and is mainly of interest in that seven lesions, apparently arteriovenous varices, were present. Wilkens' case was that of a 23-year-old woman who died of an intrathoracic hemorrhage. Excellent clinical and pathologic data are available. Three lesions were present and there were the additional findings of a patent foramen ovale and bilateral apical tuberculosis of the lungs. Rodes presented the earliest pathologic study in which the pulmonary lesions were definitely associated with the pre-mortem picture of cyanosis and polycythemia.

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‡Carried out by Janes and Shenstone.

Bower's[6] case, in which an infant died from an intrathoracic hemorrhage the day after birth, is of interest in indicating that the dilated sinusoidal vessels are part of the congenital defect and that cyanosis may not be noticeable at birth.

It was the successful surgical treatment in Hepburn and Dauphinee's case that placed emphasis on the curability of polycythemia associated with pulmonary arteriovenous fistula; similar cases, with cure by pneumonectomy, have been reported by Jones and Thompson[7] and Adams, Thornton, and Eichelberger.[8] Janes[9] reported a case with surgical cure in which local excision of three hemangiomas was carried out. Additional cases emphasizing the clinical syndrome as an entity have been described by Goldman[10] and by Makler and Zion.[11] A report of a very carefully studied patient with post-mortem examination has been published by Sisson, Murphy, and Newman.[12] The rarity of the condition is apparent from the fact that the extensive review of the pathologic conditions of the pulmonary circulation by Brenner[13] and reviews of the aneurysms of the pulmonary artery by D'Aunoy and van Haam[14] and by Boyd and McGavack[15] do not contain any references to pulmonary arteriovenous aneurysm.

Since arteriovenous fistulas in the systemic circulation present a well-known syndrome, it is worth while to compare the picture with that of a pulmonary arteriovenous fistula. Among the like effects, or similarities, one might expect the bruit, the increases of the cardiac output and the blood volume, and the dilatation of the vessels proximal to the fistula. Among the reversed or unlike effects, one would expect in cases of pulmonary fistula a high content of reduced hemoglobin in the arterial blood instead of a high content of oxyhemoglobin in the venous blood and a collapsing pulse in the hilar vessels instead of a collapsing pulse in the systemic arteries. Among the new effects, there could be predicted the effect of arterial hypoxemia, polycythemia and its consequent symptoms, hemoptysis, and the potentiality of arterial emboli from venous thrombosis.

In a case of pulmonary arteriovenous fistula it will be apparent that, since some of the blood, pumped into the pulmonary artery, will pass directly through the fistula without oxygenation, two primary circulatory faults result. The first is that the effective pulmonary flow is decreased and the second is that a mixture of venous and arterial types of blood, with a resultant arterial blood with incompletely saturated hemoglobin, is pumped into the aorta. These two conditions are those which are also present in cyanotic congenital heart disease. One might thus expect that the clinical picture of a large pulmonary arteriovenous fistula would simulate that of congenital heart disease, a tetralogy of Fallot, the severity of the symptoms in each instance being mainly dependent on the reduction of effective pulmonary flow.

An analysis of the symptoms and signs in the reported cases of pulmonary arteriovenous fistula reveals a stereotyped syndrome (Table I). The basic picture is one of cyanosis, clubbing of the fingers and toes, and polycythemia without abnormality of the heart. Dyspnea, dizziness, faintness, and thickness of the speech are common secondary symptoms. More than one-half the patients have had small capillary hemangiomas of the skin or mucous membranes. A bruit over the lung may or may not be discovered and, when present, it may or

TABLE I. SYMPTOMS AND SIGNS IN CASES OF PULMONARY ARTERIOVENOUS FISTULA

	AGE (YR.)	CYANOSIS	CLUBBING	DYSPNEA	HEMOPTYSIS	BRUIT	CARDIAC ENLARGEMENT	POLYCYTHEMIA	INCREASED BLOOD VOLUME	ARTERIAL HEMOGLOBIN (%)	ROENTGENOGRAM	LESIONS	REMARKS
Wilkens,[4] 1917	23	+		+	+	+	+				+	3	Fatal hemorrhage; necropsy
Rodes,[5] 1938	25	+	+	+	+	0	0	+			+	3	Fatal hemoptysis; necropsy
Smith and Horton,[2] 1939	46	+	+	+	0	+	0	+	+		+	1	Living, 1946
Hepburn and Dauphinee,[1] 1942	23	+	+	+	0	0	0	+	+	73	+	1	Pneumonectomy
Goldman,[10] 1943	22	+	+	+	0	0	0	+	+	70	+	1	
Adams and co-workers,[8] 1944	24	+	+	0	+	0	0	+	+	71	+	2	Pneumonectomy
Jones and Thompson,[7] 1944	24	+	+	0	0	+	0	+			+	1	Pneumonectomy
Janes,[9] 1944	30	+		0	+	+	0				+	3	Local excisions
Sisson and co-workers,[12] 1945	45	+	+	+	+	+	+	+			+	2	Necropsy
Makler and Zion,[11] 1946	20	+	+	+	0	+	0	+			+	4	
Present case	20	+	+	0	0	+	0	+	+	74	+	1	Lobectomy; well

may not have the continuous characteristics of systemic arteriovenous bruits. It may be of increased loudness in inspiration and practically inaudible on expiration. Cardiac enlargement has been present in only two cases. Its absence in other cases has been attributed to the small increase of cardiac work caused by the pulmonary arteriovenous fistulas.

The laboratory investigation has consistently revealed the presence of polycythemia, erythrocytes numbering between 6,000,000 and 8,000,000 per cubic millimeter of blood, and the hematocrit varying from 60 to 80 per cent erythrocytes. In all five cases in which the blood volume was determined it was increased to approximately twice normal value; splenomegaly, however, has been present in only two instances. The arterial hemoglobin saturation has been studied in only four cases. The fact that the percentages of the hemoglobin oxygen saturation of the arterial blood are nearly identical cannot be regarded as fortuitous. Rather it must be related to a compensatory process in the circulation, in which the arterial oxygen tension is held to a certain level by increased cardiac output. Increase of cardiac output, without parallel increase of oxygen consumption, will increase venous oxygen tension; the blood in the pulmonary artery will be less unsaturated and hence the shunted blood will have less effect in reducing the arterial hemoglobin saturation. These observations indicate that the stimulus for increased cardiac output is present until the arterial oxygen tension is approximately 40 mm. of mercury and correlate quite well with the reports indicating that cardiac output does not begin to increase under conditions of lowered oxygen pressure until the arterial oxygen tension drops to 45 to 50 mm. of mercury.[16]

In all the reported cases roentgenologic examination of the thorax has shown positive findings which may be practically diagnostic. A nodular-appearing lesion, often well shown by tomography, with pulsation when observed roentgenoscopically, and increased hilar pulsation on the side of the lesion, is the most characteristic picture. The importance of the roentgenologic examination lies not only in the diagnosis of the syndrome itself, but also in the determination of the number of lesions, for the fistulas are more likely to be multiple than single. In any plan for a surgical procedure the proper assessment of the number and size of various fistulas is of the utmost importance.

REPORT OF CASE

A college sophomore, 20 years of age, was referred to the Mayo Clinic for consideration of surgical treatment for a cyanotic disorder of the circulation.

The history, as obtained from the parents, was that the patient had been a normal-appearing baby at birth, that his development had been normal, and that it was not until he was about 8 years of age that the color of his lips was noted to be darker than that of other children. The teachers in grade school first noticed the clubbed fingers, and he complained of aching pains in the legs about this time. His early school years were uninterrupted and his scholastic record was excellent. He did not take part in school sports because of awkwardness and general inaptitude; he denied that he had shortness of breath. In recent years only after climbing three flights of stairs had he noticed shortness of breath. In recent years also he had occasional mild giddy spells with tinnitus, and, rarely, he noticed a mild frontal headache. There were no visual disturbances. For the past two years there had been an increasing amount of pain in the knee

joints and, beginning sixteen months previously, a superficial weeping ulceration of both ankles had developed. In 1941 he had an attack of "pleurisy" and was away from school three weeks.

On physical examination the most outstanding finding besides the cyanosis was the extensive clubbing of the fingers and toes and the enlargement of the wrist, knee, and ankle joints. His height was 6 feet, 2½ inches (189 centimeters), and his weight was 150 pounds (68.0 kilograms). The conjunctiva was congested and examination of the fundi revealed the retinal veins to be large, deeply cyanotic, and congested in appearance.

Examination of the heart revealed a forceful apical impulse in the midclavicular line and normally loud first and second sounds. There were no murmurs. On auscultation of the thorax over a small area below the right nipple there was a late systolic bruit, which varied in intensity, depending on the phase of respiration, being loudest in midinspiration (Fig. 1).

The spleen was enlarged and palpable at the costal margin. On the medial side of both ankles there was an area of red, moist, very superficial ulceration, similar to the stasis lesions of adults who have varicose veins and venous insufficiency of long duration.

Roentgenologic Data.—The thoracic roentgenogram showed an irregular nodular shadow in the right lung and a normal cardiac contour. Roentgenoscopic examination showed an irregular nodular pulsating mass contiguous to the inferior portion of the right hilus. The appearance was that of vascular abnormality. It was possible to obtain the thoracic roentgenogram that had been taken eight years previously when the patient was 12 years of age, and the appearance is similar (Figs. 2 and 3). On completion of the roentgenographic studies it was thought that the lesion might be confined to the right middle lobe.

The laboratory findings were confirmatory of the diagnosis of a pulmonary arteriovenous fistula (Table II).

Surgical Exploration.—In planning the surgical approach, it was hoped that right middle lobectomy might be possible, but in the event that this was impossible, or if the right middle lobe was not the site of the vascular abnormality, pneumonectomy was to be attempted. In order to measure the volume of the pulmonary arteriovenous shunt, it was planned at operation to take samples of blood simultaneously from a branch of the pulmonary artery and the radial artery. Additional samples were to be obtained from the superior pulmonary vein, if possible, or from the radial artery after the shunt was closed.

Exposure was obtained by an incision around the right scapula and resection of a long segment of the sixth rib. There were no pleural adhesions except between the middle lobe and the thoracic wall, where there were many tortuous vessels apparently communicating with the pulmonary circulation. Both the internal mammary artery and veins were several times normal size. There was a palpable thrill over the middle lobe. Dissection was carried down into the hilus and a large vessel, ostensibly a greatly dilated pulmonary artery to the middle lobe, was isolated, a specimen of blood was taken, and the vessel was ligated. Dissection of the hilus was continued, and when connections to the lobe were severed, it became apparent that a large quantity of blood was entering the lobe from the collateral vessels in the thoracic wall. The lobe became more and more congested. Separation of the lobe from the thoracic wall was accompanied by severe bleeding, and for a time it appeared as if the patient might die on the table from hemorrhage. The hemorrhage was finally controlled by mattress sutures, multiple ligatures, and oxidized cellulose gauze soaked in thrombin. The thorax was closed after the lung had been inflated, two catheters being inserted in the thorax for temporary closed drainage.

During the latter part of the operation, the patient received 7 liters of blood, 1 liter of which was his own blood which had been removed in two venesections during the period of the medical investigation.

The postoperative course was quite smooth. The catheter drains were removed on the fifth day. The patient was allowed up on the sixth day and was dismissed from the hospital on the twelfth postoperative day and from the clinic on the seventeenth day.

Pathologic Data.—The pathologic specimen consisted of the right middle lobe with a long hilar region where the cut ends of three vessels and two bronchi could be identified. The lobe could be roughly divided into two portions, a medial half, which could be inflated and which

appeared normal, and a lateral half, which could not be inflated but consisted of a mass of twisted varicose vessels. Intercommunications were frequent and injection with radiopaque paraffin was carried out. Long, looped, and blind-ended vascular sinuses up to 1 cm. in diameter were demonstrated, but any efforts to demonstrate discrete intercommunications between artery and vein were unsuccessful. With only a lobe to investigate, it was not possible to ascertain which

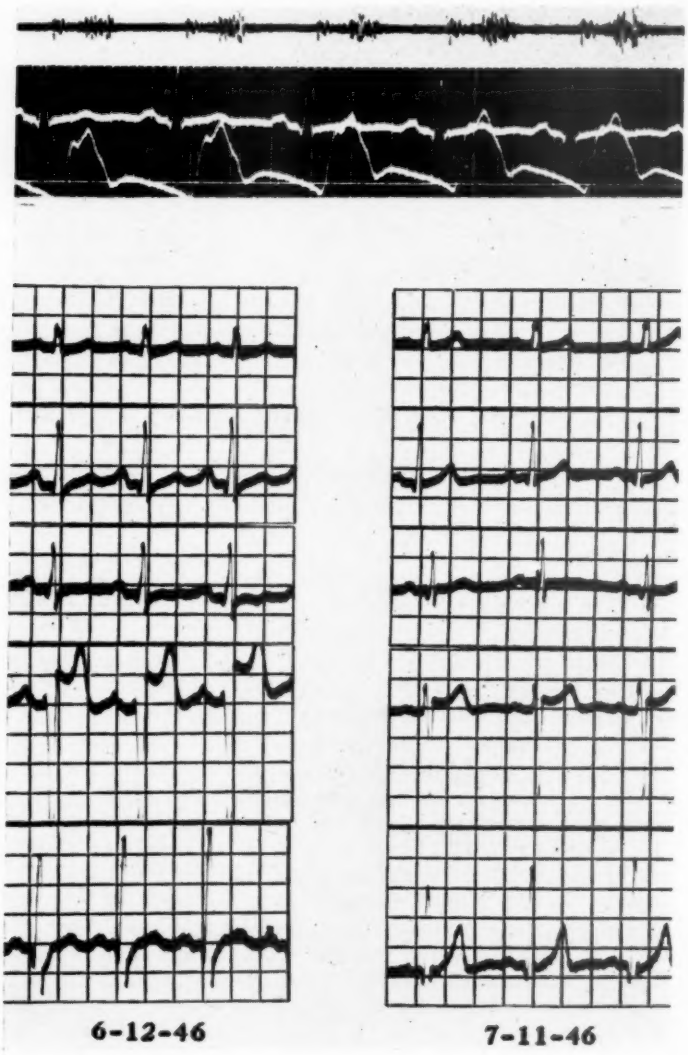

Fig. 1.—The phonocardiographic tracing in the upper figure shows the graphic representation of the late systolic bruit recorded with the microphone placed below the right nipple. The carotid pulse is shown below; Lead II of the electrocardiogram, in the middle. Phonocardiograms taken over the precordium showed normal heart sounds only. Electrocardiograms with precordial leads CR_2 and CR_5 taken preoperatively and sixteen days after operation are shown below. In the semidirect right ventricular lead there is an increase in the height of the R wave and a marked decrease in the segment elevation after operation, while in CR_5 there is practical disappearance of the S wave and increase in height of the T wave. Ten weeks after operation the electrocardiographic tracings were similar to those made sixteen days after operation.

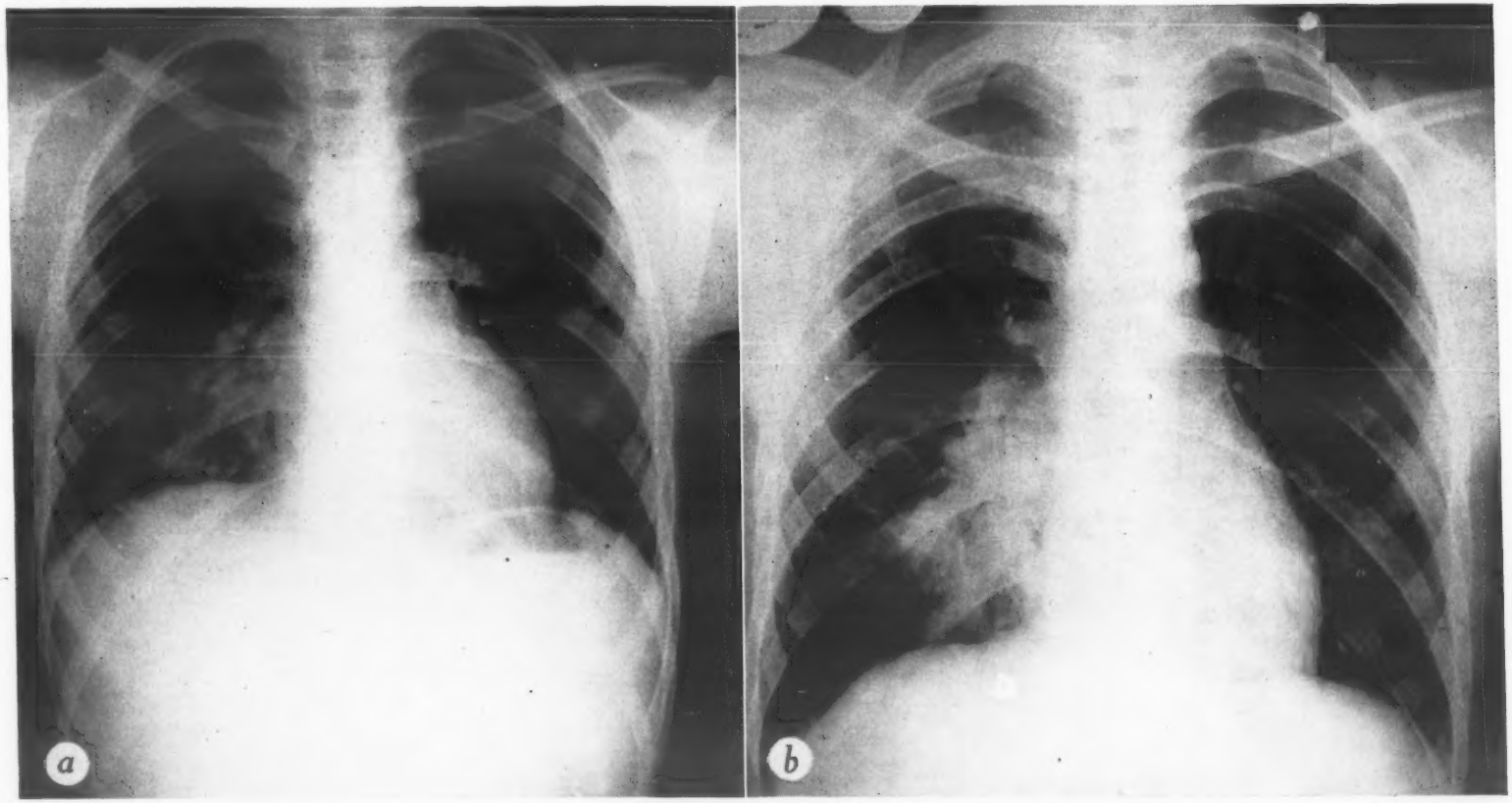

Fig. 2.—Roentgenograms in a case of pulmonary arteriovenous fistula. *a*, Taken eight years previously when patient was 12 years of age. *b*, Taken preoperatively. The lesion appears more dense in *b* than in *a*. The lobulated character of the lesion is particularly important.

blood vessel at the hilus was artery and which was vein. While some vessels over the surface of the lung were tied off previous to injection, none of the huge vessels in the pulmonary lesion appeared to communicate directly with the thoracic wall.

Histologic examination did not reveal neoplastic tissue and the blood vessels and sinuses all had elastic tissue and some muscle in their walls. That the blood sinuses had acquired arterial characters throughout the years is somewhat speculative; yet the histologic appearance was similar to that of a vein subjected to high luminal pressure over a considerable length of time. The vacuolization of the media, fragmentation of the internal elastic lamina, and some irregular intimal proliferation with muscle appearing in the intima through clefts of the elastic membrane are characteristic of thickened veins.

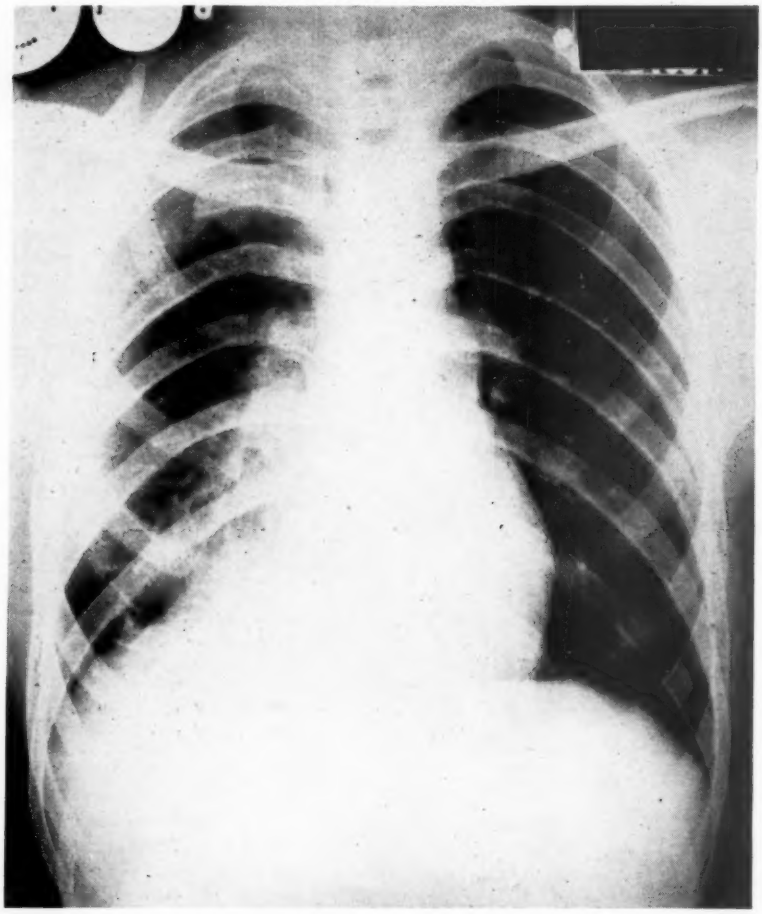

Fig. 3.—Roentgenogram in a case of pulmonary arteriovenous fistula taken ten weeks after operation. The diaphragm in the preoperative (Fig. 2, *b*) and postoperative roentgenograms is at the same height. While the right border of the heart is difficult to identify in each instance, it seems apparent that the size of the heart has decreased. The frontal cardiac area as determined by tracings on graph paper was 84 sq. cm. preoperatively and 68 sq. cm. postoperatively, which would appear significant and greater than the change that could be attributed to different phases of the cardiac cycle or to a different position of the heart.

TABLE II. LABORATORY DATA IN A CASE OF PULMONARY ARTERIOVENOUS FISTULA

	PREOPERATIVE	FIFTEEN DAYS AFTER OPERATION	TEN WEEKS AFTER OPERATION
Hemoglobin (Gm.*)	24.1	11.9	14.8
Erythrocytes (per c. mm. blood)	7,590,000	4,060,000	5,180,000
Hematocrit (per cent)	82	44	48
Blood volume (c.c. per kg.)	172	115	87
Plasma	37	64	45
Erythrocytes	135	51	42
Oxygen capacity (c.c.)	30.8	14.8	20.2
Oxygen content (c.c.)	22.8	13.7	19.0
Hemoglobin saturation (per cent)	74	93	94.1
Plasma protein (Gm. per 100 c.c. serum)	8.9	6.5	7.3
Albumin/globulin ratio	2.2/1	1.4/1	
Sodium (meq. per liter serum)	145	137.5	132
Potassium (meq. per liter serum)	4.8	4.3	4.1
Calcium (meq. per liter serum)	5.8	4.7	4.9
Carbon dioxide combining power (Vol. per 100 c.c. plasma)	48.6	60.6	65.2
Uric acid (Mg. per 100 c.c. of blood)	3.9		4.2
Basal metabolic rate (per cent)	−13		−13
Vital capacity (liters)	3.82		3.10
Venous pressure (Cm.)	11		11
Circulation times (sec.)			
Decholin	20		12
Ether	10		8

*Photelometric determinations.

COMMENT

The specimens of blood taken at the time of the operation were without value in determining the volume shunt through the fistula, for the blood from the radial artery was 100 per cent saturated both before and after the hilar vessels were tied. This finding might be explained by two possibilities: either the shunt was functionally closed or the volume flow through it of venous blood of relatively high oxyhemoglobin content was sufficiently small so that this blood could be later oxygenated by the oxygen in solution in the blood. The actual oxygen tension in the lungs is unknown because of the unknown ether tension. The patient was under nitrous oxide ether anesthesia, 5 to 10 mm. of mercury positive pressure, and the alveolar oxygen tension would be approximately 550 mm. less the tension of the ether vapor. It is possible that the fistula might have closed

as a result of the operative pneumothorax. While this explanation would fit the observation that the bruit had disappeared during expiration in the original examination, it is not in accord with the operative finding of a thrill over the varicose vessels. An alternative explanation to a closure of the fistula is that the varicose vessels were draining through collateral veins to the thoracic wall and to the right side of the heart. The operative blood specimen taken from the large pulsating vessel entering the middle lobe, believed to be pulmonary artery, showed a hemoglobin saturation of 92.5 per cent. That this represents the hemoglobin saturation of mixed venous blood seems doubtful, but with such high hemoglobin content of the blood and high alveolar oxygen tension in the alveoli, it might be possible, the cardiac output being in the range of 10 to 12 liters per minute. It is possible that the high saturation of the sample could occur from reflux from a pulmonary vein, or a bronchial artery, or an intercostal artery communication. In view of the definite enlargement of the internal mammary artery, the last possibility is considered a most likely cause of the probable arterialization of the sample.

Whether the congenital vascular abnormality was originally confined to the lung proper is impossible to state; our opinion, based on the findings of other cases, is that it was. The thoracic wall attachment is believed to be a secondarily acquired condition, perhaps occurring at the time of the patient's pleurisy five years previously.

The term used for the other cases that have been reported has been either cavernous hemangioma or simply arteriovenous fistula. Any term should take into account the following factors: the congenital nature and multiplicity of the lesions; the large dilated-appearing vascular sinuses being part of the congenital defect and not entirely the result of secondary dilatation; and the frequent association of the lesion with other small vascular nevi of the skin and mucous membranes. While the term congenital arteriovenous angioma seems permissible, the preferred term to us is congenital arteriovenous varix.

The general physique of our patient resembled that of the patient in at least one of the other reported cases, but it seems doubtful whether the tall stature with long limbs could be a result of the pulmonary lesion. The ratio of his sitting height (38¼ inches, or 97 centimeters) to his standing height (74½ inches, or 189 centimeters) is not abnormal for university students.[17]

It may be noted that the carbon dioxide combining power, or alkali reserve, was of a low normal value before operation, a fact which is in accord with primary loss of carbon dioxide under conditions of hypoxemia. This has been pointed out by Adams and associates[8] as occurring in their patient associated with a low serum sodium. In contrast to their observation of apparent loss of base, our patient did not show evidence of loss of sodium. In fact, if serum magnesium levels were normal, he had a high normal value for the total base of the serum or serum water. Following restoration of a normal circulatory system, the values for the carbon dioxide combining power and serum cations changed to more average values. Since the basal metabolic rates were determined by collection of expired air, it was possible to re-examine the basic data for ventilation rates. Previous to operation the respiratory minute volume (expired air, saturated

20° C.) was 6.17 liters per minute with a respiratory quotient of 0.73, and after operation it was 5.48 liters per minute with a respiratory quotient of 7.3. The basal oxygen consumption preoperatively was 246 c.c. per minute; ten weeks postoperatively it was 243 c.c. per minute, and it is believed that the difference in respiratory minute volume is significant and consistent with the change in carbonate of the plasma. One thus has evidence of the same type of respiratory compensation to a lowered arterial oxygen tension of intrinsic causation as occurs with diminished oxygen tension in the environment of high altitudes.

FOLLOW-UP STUDY

At the time of his dismissal from the clinic, seventeen days after operation, the patient was feeling well, his color was normal, no bruit was present over the thorax, and he was judged to be cured. The stasis dermatitis had practically healed. The hemoglobin saturation was 93 per cent. The blood volume had not yet returned to normal and there was a relative and absolute increase in the plasma volume, perhaps a compensatory mechanism to fill the large vascular bed.

He returned to the clinic for reinvestigation on September 16, approximately ten weeks after operation, at which time he was feeling well and without complaints. His fingers and toes were little changed in shape, but there was a deep transverse groove near the base of the nails. He had not indulged in any strenuous activity and had not noticed any change in his exercise tolerance. The dermatitis of the ankles had completely healed, leaving a soft skin, normal in appearance, except for a mild degree of pigmentation. While the cardiac size, determined roentgenologically, had been well within normal limits previous to operation, there was some decrease in the roentgenographic shadow ten weeks after operation (Fig. 3). The laboratory findings were normal (Table II). There had been a slight decrease in the vital capacity, which is believed to be a temporary change.

SUMMARY

The clinical syndrome, consisting of cyanosis, clubbing of fingers, and polycythemia related to pulmonary arteriovenous fistula, is discussed and the importance of the diagnosis in view of the availability of surgical cure is emphasized.

The first case with the unusual complication of collateral circulation to the thoracic wall and with surgical cure by lobectomy is presented. It is believed that this is the ninth case of pulmonary arteriovenous fistula to be recognized clinically and reported and the fifth patient to be cured by surgical treatment.

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THE EFFECT OF CYANIDE ON THE ELECTROCARDIOGRAM OF MAN

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MEDICAL CORPS, ARMY OF THE UNITED STATES

STUDIES on the effect of cyanide on the electrocardiogram of man were undertaken, at first, in conjunction with experiments on therapy of cyanide poisoning. The preliminary observations on the effect of small doses of sodium cyanide were of sufficient interest to warrant an extension of the study. Although clinical observations, described in case reports by Lambert[1] and Williams,[2] indicated involvement of the cardiovascular system in serious or fatal cyanide poisoning, electrocardiographic tracings were not recorded.

The effect on the electrocardiogram of man given intravenous doses of sodium cyanide just sufficient to stimulate respiration was studied in sixteen normal soldiers. A dose of 0.11 mg. of sodium cyanide per kilogram of body weight, which is generally given intravenously in determining arm-to-carotid body circulation time, frequently failed to stimulate respiration. Therefore, it was necessary to inject 0.15 mg. and, in some instances, 0.2 mg. of sodium cyanide per kilogram of body weight to elicit respiratory stimulation.

The effect of lethal doses of cyanide was studied by recording continuous electrocardiographic tracings on four men executed by the inhalation of hydrocyanic acid.

RESULTS

The electrocardiograms of fifteen of the sixteen men who received 0.11 to 0.2 mg. of sodium cyanide per kilogram of body weight revealed a sinus pause, without evidence of auricular activity, which persisted for 0.88 to 4.2 seconds. In some instances nodal escape occurred before auricular activity was re-established. This sinus pause immediately preceded or accompanied the respiratory stimulation. Immediately after the pause, there were marked sinus irregularity and a slowing of heart rate for periods ranging from a few seconds to as long as two minutes which, in turn, were followed by a gradual acceleration to rates above the control levels. Control heart rate and rhythm were generally restored within three minutes. Figs. 1 to 4 illustrate these changes. The sixteenth subject failed to show a sinus pause and exhibited only a slight acceleration in heart rate at the time of respiratory stimulation.

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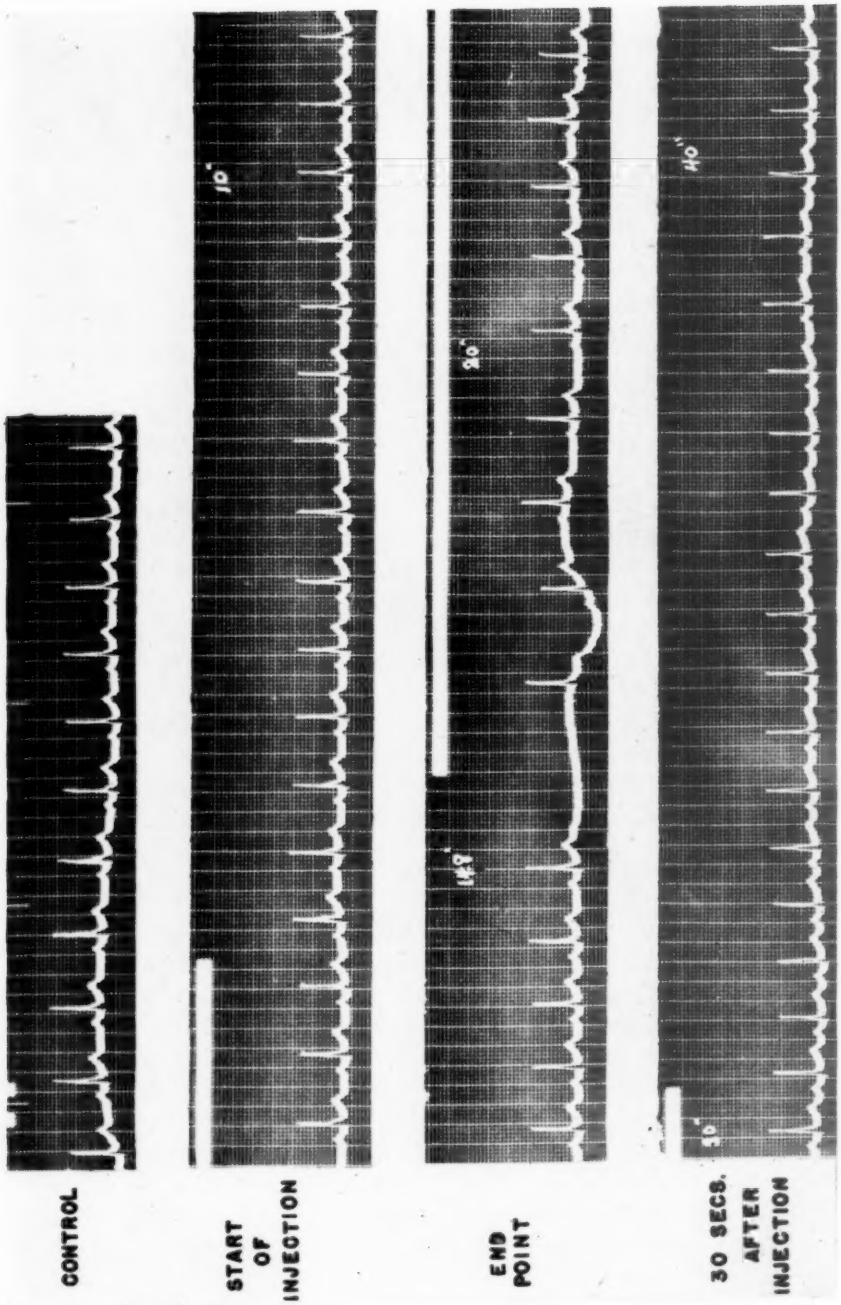

Fig. 1.—Subject B. L. Given 0.15 mg. sodium cyanide per kilogram of body weight. End point at 14.8 seconds. Sinus pause for 2.8 seconds. Nodal escape at 1.92 seconds.

Ventricular complexes have been retouched in this and most of the subsequent figures.

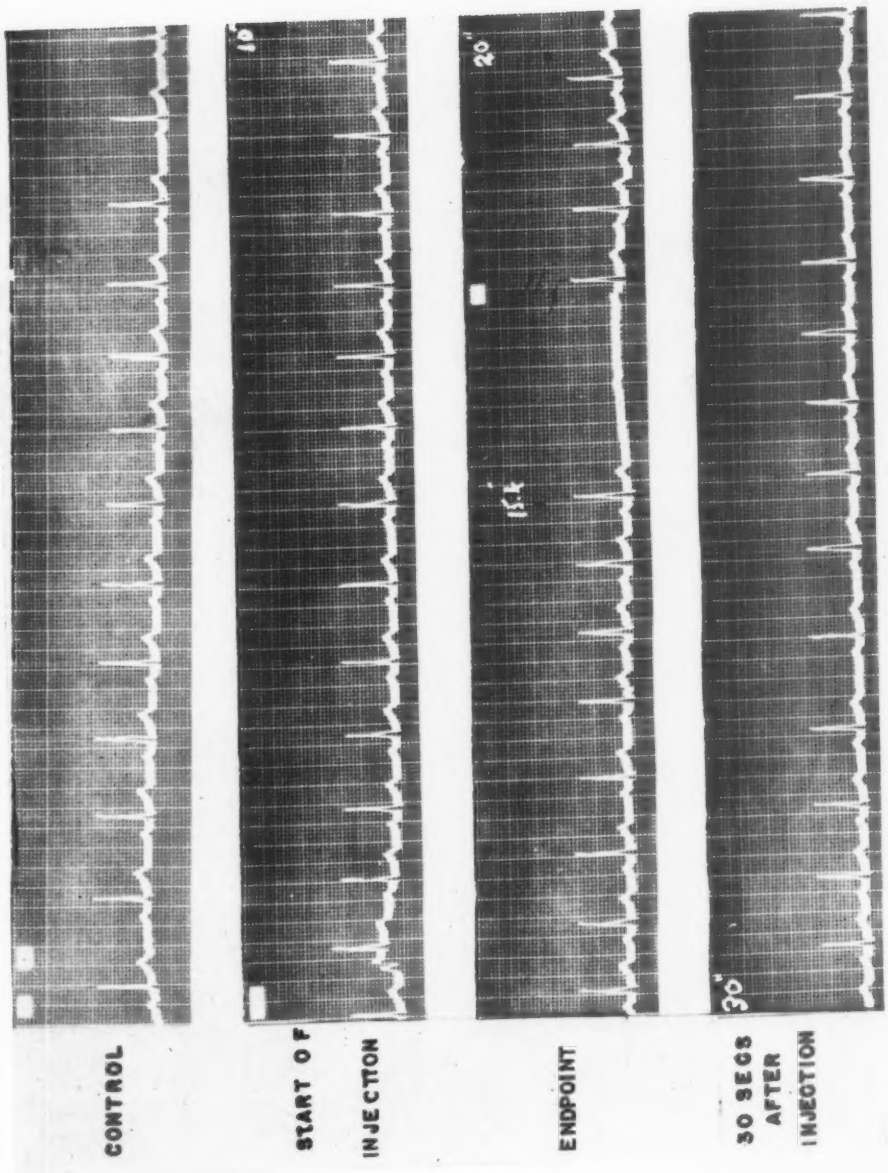

Fig. 2.—Subject G. U. Given 0.15 mg. sodium cyanide per kilogram of body weight. End point at 15.4 seconds. Sinus pause for 2.2 seconds.

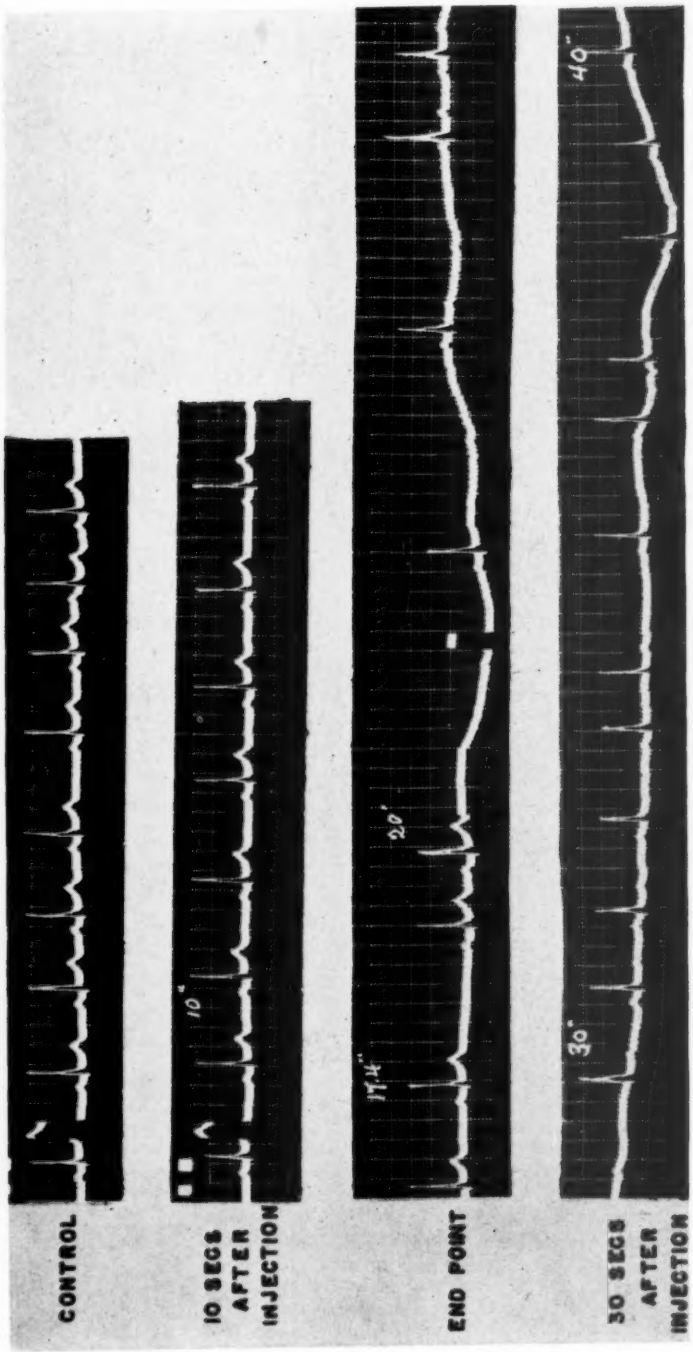

Fig. 3.—Subject O. N. Given 0.2 mg. sodium cyanide per kilogram of body weight. End point at 17.4 seconds. Marked sinus slowing and irregularity for approximately one minute.

The four men executed by inhalation of hydrocyanic acid exhibited striking electrocardiographic aberrations. The records of three of the four subjects are shown in Figs. 5*A*, 5*B*, 6*A*, 6*B*, 6*C*, 7*A*, and 7*B*.

"Control" records obtained after the men were strapped in the execution chair, but before the hydrocyanic acid was generated, revealed initial heart rates varying between 102 and 166 beats per minute.

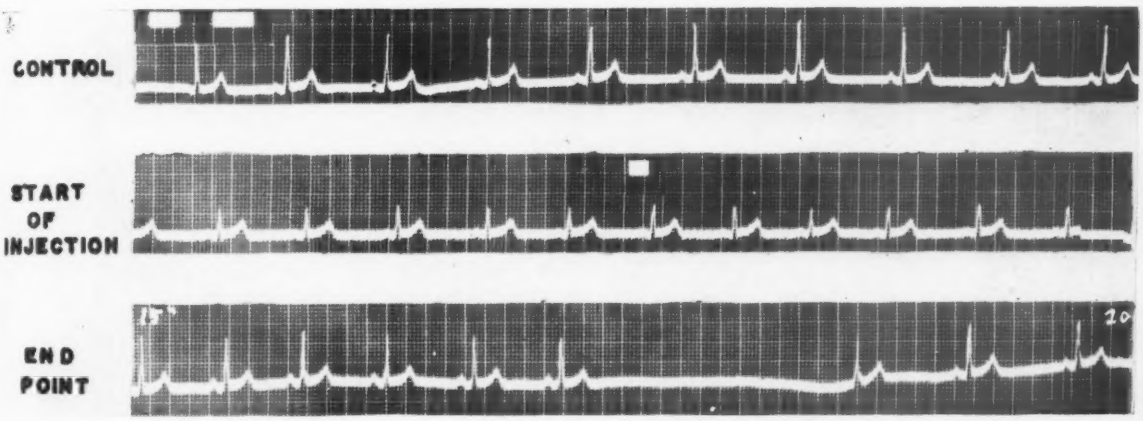

Fig. 4.—Subject M. O. Given 0.2 mg. sodium cyanide per kilogram of body weight. End point at 19.2 seconds. Sinus pause for 4.2 seconds. Nodal escape at 3.2 seconds. (Control and end point in Lead II; start of injection in Lead I.)

All four subjects revealed a marked slowing of heart rate which reached its nadir between the first and third minutes. This slowing was accompanied by sinus irregularity and eventually by complete disappearance of P waves. During the period of auricular arrest, the rhythm was auriculoventricular nodal in two and idioventricular in the other two subjects. A secondary increase in rate, but not to "control" levels, was observed during the third and fourth minutes along with the irregular reappearance of P waves, some of which were not conducted. All subjects showed A-V dissociation with a secondary decrease in rate during the fifth minute (Fig. 6*B*). During the sixth and seventh minutes, the heart rate again showed a slight increase and a return to normal sinus rhythm.

Thereafter, the heart rate slowed progressively. Normal A-V conduction in one man and A-V conduction with incomplete A-V block in a second were maintained throughout the period of observation (approximately thirteen minutes). A third subject developed Wenckebach's phenomenon, 2:1 block, and, finally, complete heart block. The fourth subject maintained normal A-V conduction until the fourteenth minute, when he developed ventricular tachycardia and ventricular fibrillation (Fig. 7*B*).

The QRS complexes exhibited marked changes in voltage and form. Since these changes were accompanied by changes in rhythm and rate, and by changes in position of the subjects, incident to slumping and twisting, their significance is obscure. One subject exhibited transitory right axis deviation (Fig. 5*A*). Intraventricular conduction time was normal except in two subjects during periods of idioventricular rhythm (Fig. 6*A*).

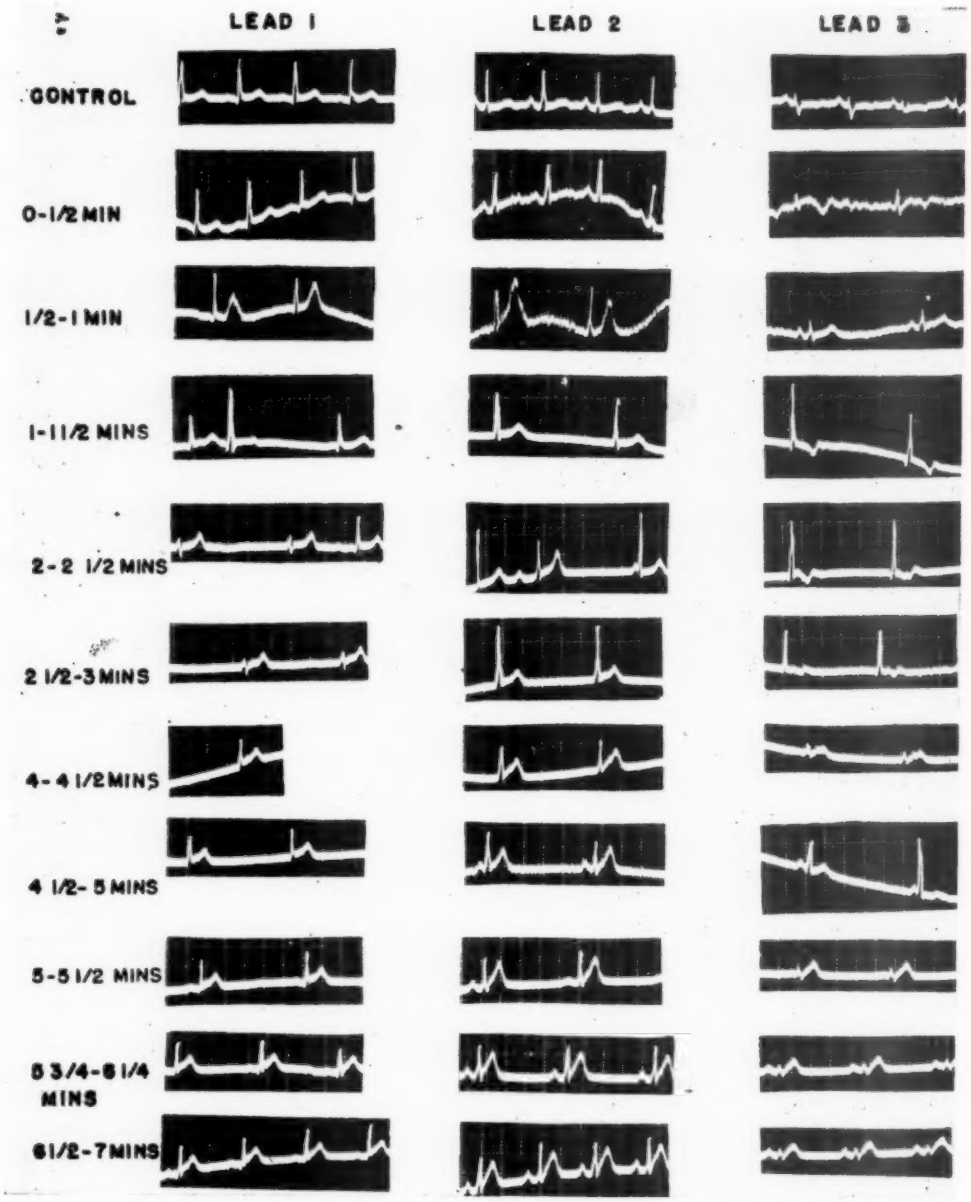

Fig. 5A.—Subject X. *0* time indicates start of execution.

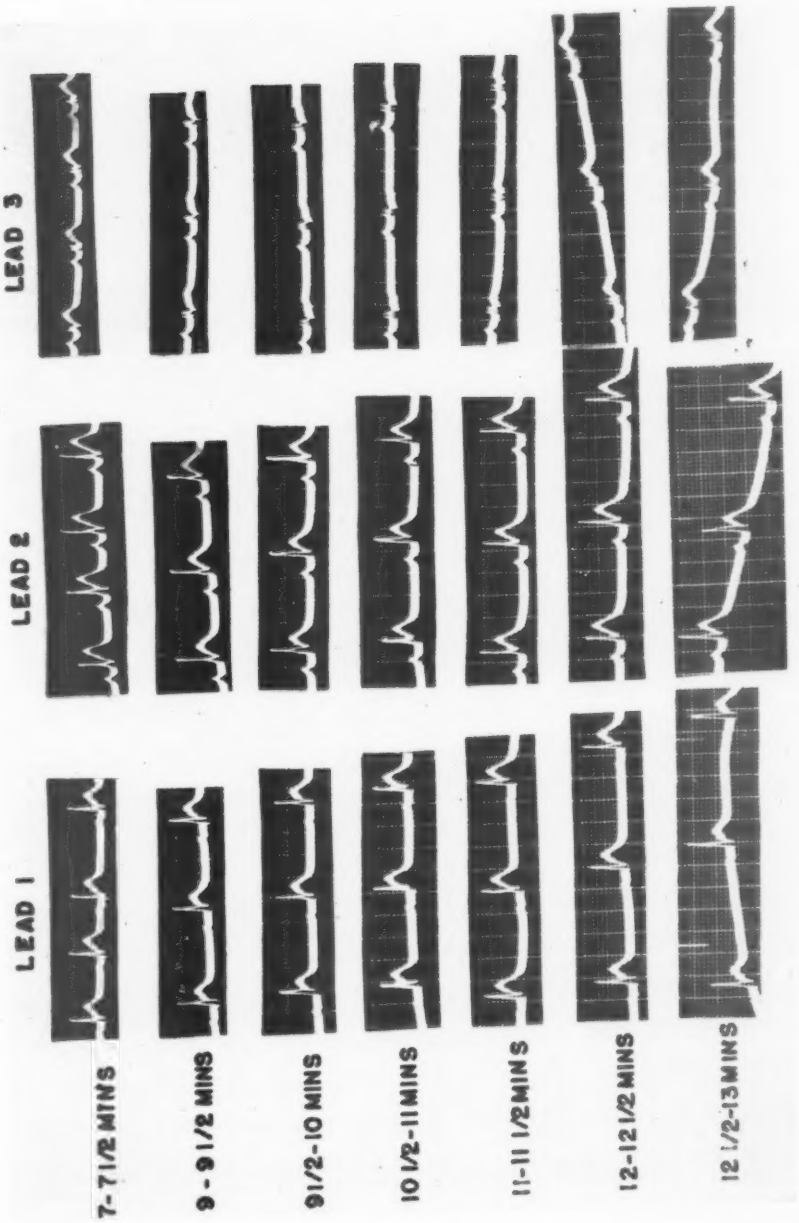

Fig. 5*B*.—Subject X. Recording was discontinued at thirteen minutes.

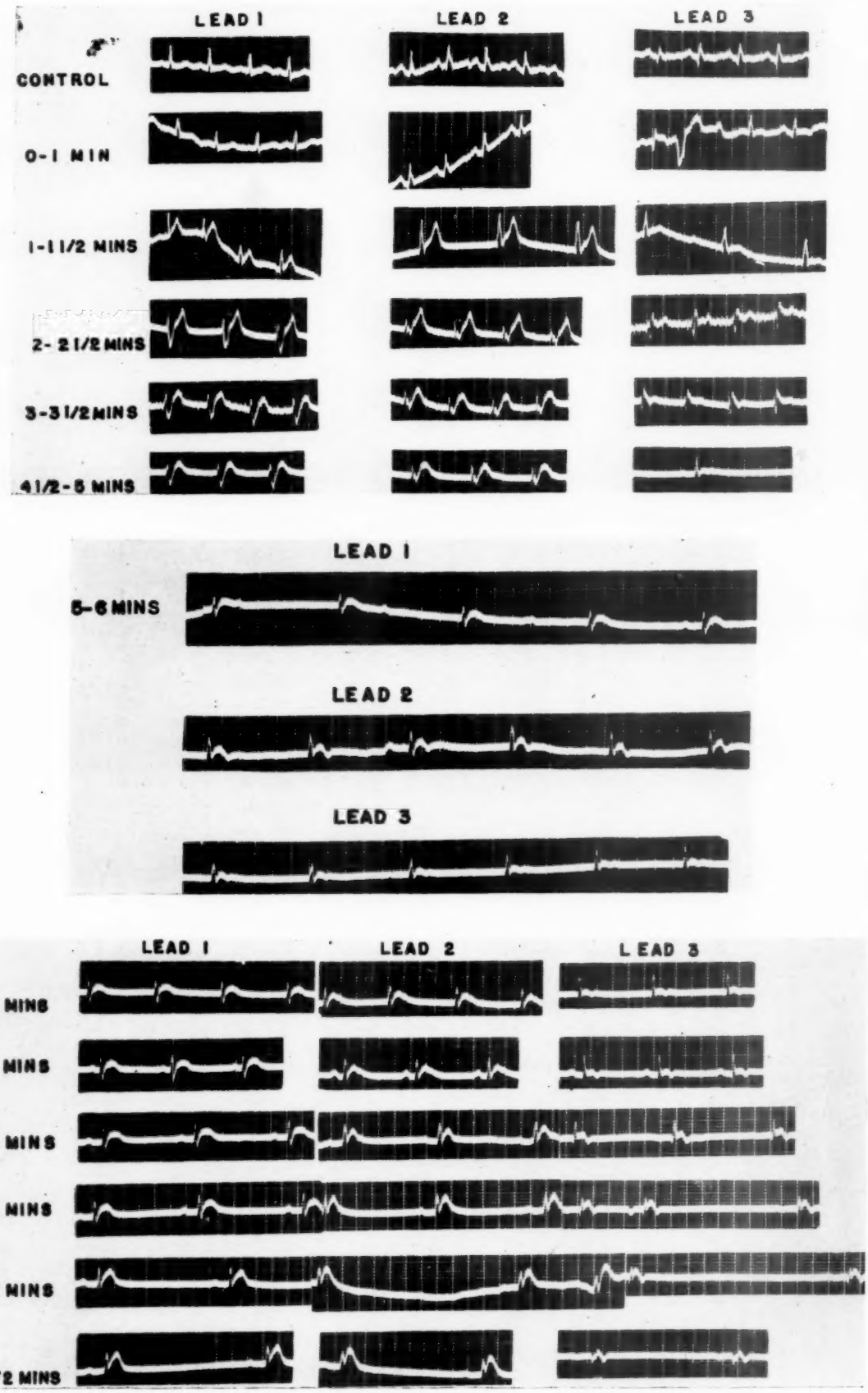

Fig. 6.—Subject Y. *0* time indicates start of execution. Asystole for five seconds.

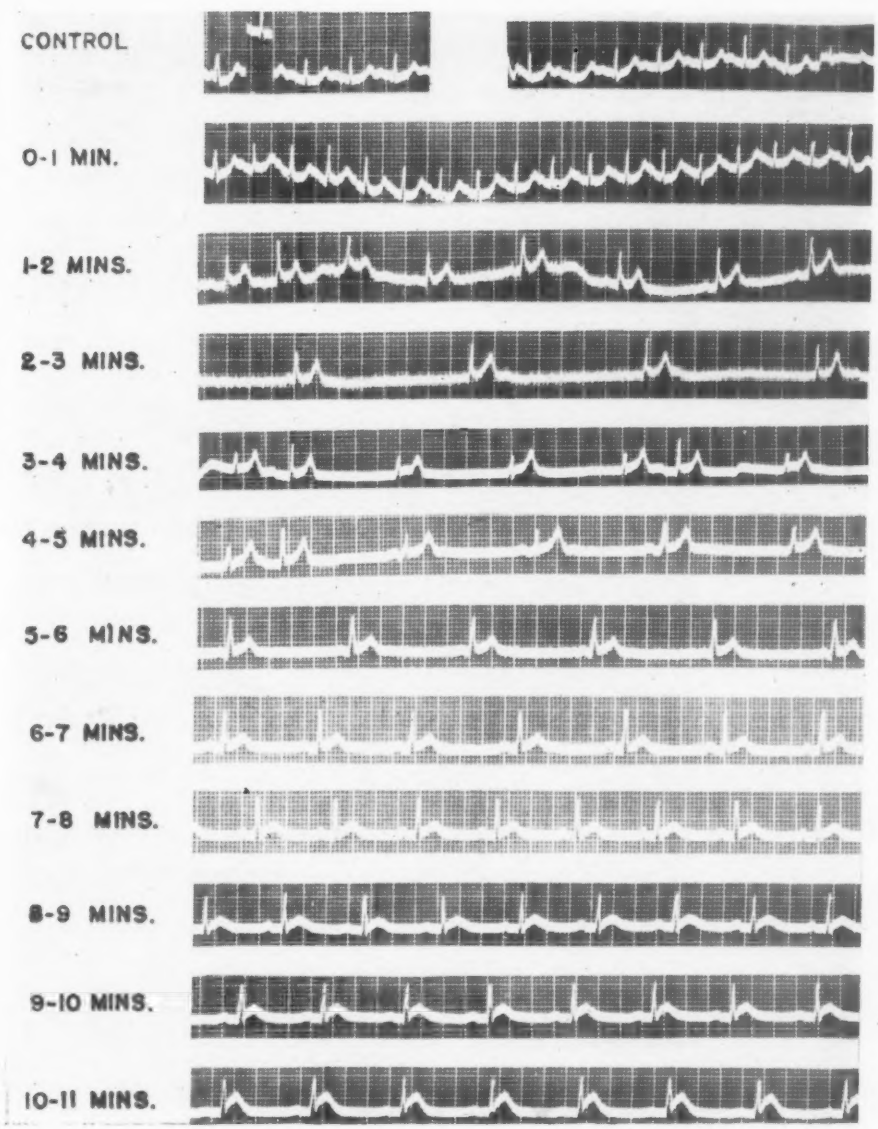

Fig. 7*A*.—Subject Z. All tracings recorded in Lead I.

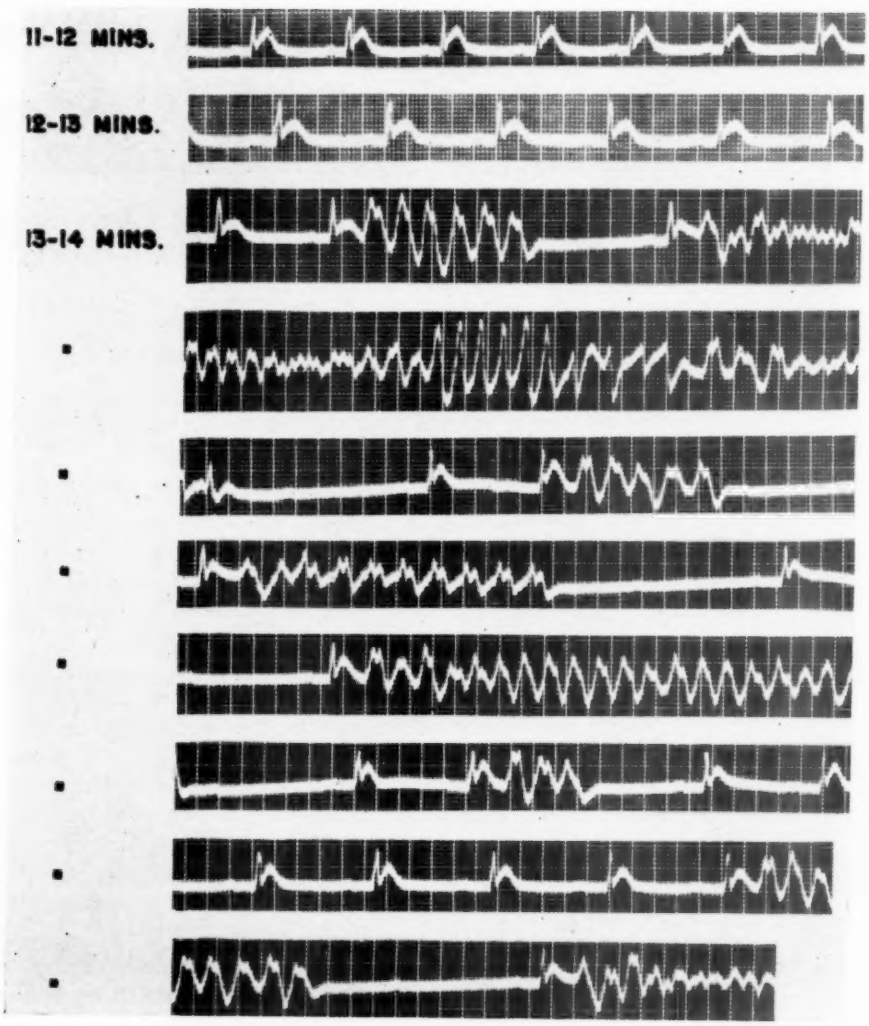

Fig. 7*B*.—Subject Z. All tracings recorded in Lead I.

T waves showed an early but transient increase in amplitude (most marked in the subject whose tracings are shown in Fig. 5*A*). There was progressive shortening to the point of disappearance of the S-T segments. Terminally the T waves originated high on the R wave.

DISCUSSION

The mechanisms responsible for the changes which have been described are complex. The following factors play a role:

1. Reflex stimulation of the cardioinhibitory, cardioaccelerator, and vasomotor centers via the carotid and aortic bodies.
2. The central action of cyanide on the cardiac and vasomotor centers.
3. The direct toxic effect of cyanide on the heart.
4. The additive effect of anoxia due to respiratory arrest.

In dogs, the early changes in rhythm and rate which are similar to those observed in man[3] can be diminished by atropine or abolished by bilateral vagotomy and denervation of the carotid body. Thus, the early changes are neurogenic and are due to reflex or central effects of cyanide, whereas the late changes are due to the direct toxic action of cyanide on the heart plus the effect of anoxia.

The electrocardiographic changes observed with small doses of sodium cyanide (periods of asystole varying from 0.88 to 4.2 seconds) offer a possible explanation for the untoward and, at times, alarming reactions which have occasionally been observed when sodium cyanide is injected intravenously for determination of arm-to-carotid body circulation time. It is possible that in the presence of organic heart disease alterations in rhythm and rate resulting from a small dose (0.11 mg. per kilogram of body weight) of sodium cyanide may be even more striking than those observed in our normal subjects. One of our subjects (Fig. 4) had momentary dim-out during the test.

SUMMARY

1. The electrocardiographic changes resulting from intravenous injection of small doses of sodium cyanide and from inhalation of lethal doses of hydrocyanic acid are described.

2. The mechanisms by which these effects are produced are discussed.

3. The period of asystole which results from small doses of sodium cyanide (0.11 to 0.2 mg. per kilogram of body weight) even in normal hearts is offered as a possible explanation for the untoward and, at times, alarming reactions which have been observed when sodium cyanide is used to determine arm-to-carotid body circulation time.

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CIRCULATORY BLOOD VOLUME OF SOME ORGANS

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AS FAR as I know, no previous attempts have been made to ascertain, on living human beings during a surgical operation, the amount of circulating blood in one of the lungs or in the spleen. On the other hand, Grosse-Brockhoff and Molineus[1] and Asmussen,[2] by means of the carbon monoxide method, have determined the amount of circulating blood in the lower extremities. The circulation to a part of the lower limbs was occluded by the application of pneumatic cuffs around the thighs. The quantity of circulating blood in the rest of the body was then determined by both the dye method and the carbon monoxide method. After this, the cuffs were deflated and new samples of blood were taken for analysis. Asmussen found that the circulating blood volume through the lower limbs below the cuff amounted to 1 liter, or 17.3 per cent of the total circulatory blood volume. As pointed out by Asmussen, certain pronounced sources of error are inherent in both the dye method and the carbon monoxide method. The chief error in the latter method is the result of the fact that myoglobin absorbs carbon monoxide.

The method elaborated by Hevesy and his collaborators[3,4] for labelling red blood corpuscles with radioactive phosphorus has made possible certain studies of the circulatory system which had been impossible before. When labelled blood corpuscles are injected intravenously into a normal person, mixture with the circulating blood soon takes place;[5-7] in some instances, within less than one minute after the injection and, in almost every other instance, in less than five minutes. After mixing has been accomplished, the injected blood corpuscles maintain their activity at a constant level long after the injection, even up to one hour. This important phenomenon renders a study of experimental changes in circulatory conditions possible within one hour. Hitherto, no method offering similar advantages has been at our disposal.

METHOD

Eight cubic centimeters of blood taken from the patient by venous puncture are shaken in a water bath at a temperature of 37° C. for two hours with radioactive disodium acid phosphate containing about 0.05 millicuries of radioactive phosphorus. A small amount of heparin is added to this compound to prevent

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blood clotting. Half of the labelled blood is then reinjected into the patient on whom studies are to be made during operation. The other half of the blood is measured with regard to its activity on plasma as well as on corpuscles. Determination of the hematocrit values is carried out simultaneously on samples of blood from the patient. Just before injecting the tagged erythrocytes into the circulatory system, the surgeon occludes the circulatory passage to one of the lungs. After the injection of the labelled blood into the patient, who is undergoing pulmonectomy or splenectomy during anesthesia, a certain fixed time is allowed to elapse in order to obtain a mixture of the labelled blood corpuscles and the circulating blood. Several samples of blood are drawn from the patient before circulation to the occluded organ is released, four to twenty-four minutes after the injection of the labelled blood. During this comparatively long period of time required for the mixing, care must be taken to maintain a constant level of the activity of the circulating blood. After this, the circulation to the occluded organ (the lung or the spleen) is released and new blood samples are taken by venous puncture up to one hour after the injection of labelled blood. All of the samples, to which a small amount of heparin has been added, are then centrifuged and the plasma removed. Finally, the blood corpuscles are weighed, dried and pulverized, and their activity measured.

RESULTS

In the present investigation, three cases were subjected to extirpation of one lung because of bronchogenic carcinoma. In a fourth case, a normal person, the circulation to the lower limbs was occluded by pneumatic cuffs around the thighs for the purpose of studying the circulating volume of blood in the lower part of the limbs.

Determination of Circulatory Blood Volume of One Lung Before Lung Extirpation in Three Cases of Bronchogenic Carcinoma.—

CASE 1.—After thoracotomy and exploration of the left lung, the pulmonary artery to this lung was occluded. Immediately afterwards, the patient's own labelled corpuscles were injected intravenously. The surgeon then waited while all the samples of blood from a brachial vein of the patient were taken. Several samples were drawn from the fourth to the seventeenth minute after the injection of the tagged erythrocytes. Eighteen minutes after the injection the pulmonary artery to the lung concerned was released, and new specimens of blood were collected up to twenty-five minutes after injection. All the samples were measured with regard to their activity by means of the Geiger equipment. The results are illustrated in Fig. 1. From this diagram, it may be seen that the specific activity of the blood samples during the time when the left lung was cut off from circulation was remarkably constant and, furthermore, that the circulating corpuscle volume in the rest of the body amounted to 2,184 Gm., or 2,359 cubic centimeters. The total circulating blood volume was calculated to equal 5,904 c.c., with a hematocrit value of 0.40. After release of the pulmonary artery to the left lung, the specific activity decreased under the influence of dilution by the blood blocked in the lung. The circulatory blood corpuscle volume, accordingly, increased to 2,550 Gm., or 2,752 c.c., and the total circulatory blood volume to 6,882 cubic centimeters. Thus, the circulatory blood volume of the left lung amounted to 978 c.c., or 14.3 per cent of the total circulating blood volume.

CASE 2.—After thoracotomy and exploration of the left lung, the vessels leading to the same lung were occluded and tagged erythrocytes were injected intravenously. Blood samples were

then collected four and twelve minutes later. Immediately after the blood samples were obtained, the vessels were released and a new series of blood samples were taken. The values of the specific activity of the samples are recorded in Fig. 2. As in Case 1, the specific activity had become almost constant before the release of the circulation to the left lung. After the circulation had been restored, the activity decreased and attained a constant level from the sixteenth to twenty-fifth minute after the injection of the labelled corpuscles. The circulating corpuscle

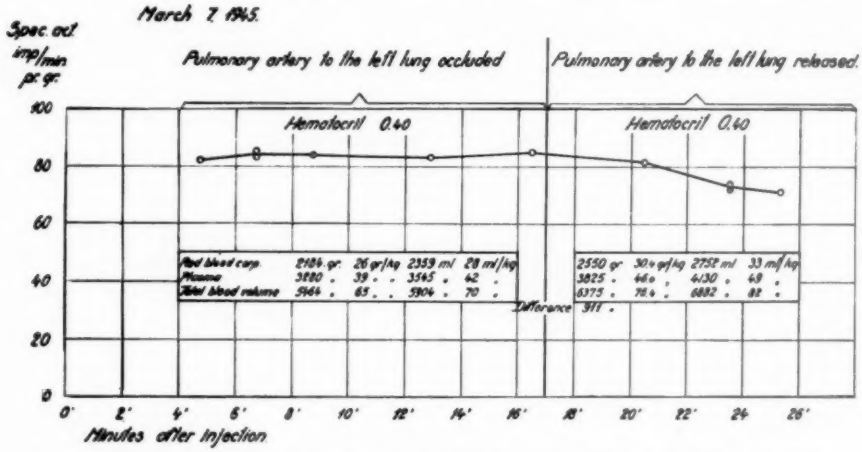

March 7 1945.
Spec. act. imp/min pr gr.
Pulmonary artery to the left lung occluded
Pulmonary artery to the left lung released.
Hematocrit 0.40
Hematocrit 0.40
Minutes after injection

Fig. 1.—Case 1. Determination of the circulating blood volume of one lung. See text.

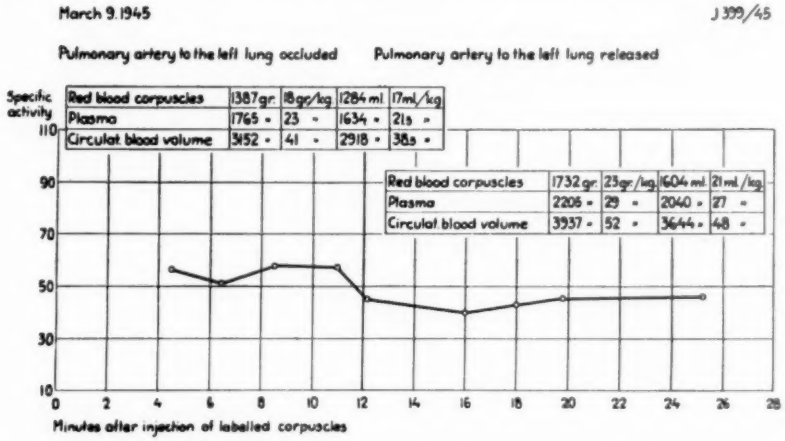

March 9.1945
J 399/45
Pulmonary artery to the left lung occluded
Pulmonary artery to the left lung released
Specific activity
Red blood corpuscles 1387 gr. 18 gr/kg 1284 ml 17 ml/kg
Plasma 1765 " 23 " 1634 " 21 "
Circulat blood volume 3152 " 41 " 2918 " 38 "
Red blood corpuscles 1732 gr. 23 gr/kg 1604 ml 21 ml/kg
Plasma 2206 " 29 " 2040 " 27 "
Circulat blood volume 3937 " 52 " 3644 " 48 "
Minutes after injection of labelled corpuscles

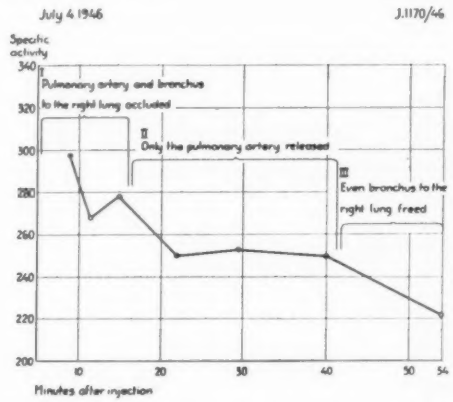
Fig. 2.—Case 2. Determination of the circulating blood volume of one lung. See text.

volume was calculated to equal 1,387 Gm., or 1,284 c.c., while the circulation to the lungs was blocked. These values were 1,732 and 1,604, respectively, when the circulation was released. During occlusion of the vessels to the left lung, the total circulatory blood volume amounted to 2,918 c.c.; when the circulation was restored, this value became 3,644 cubic centimeters. The difference was calculated to be 20 per cent. This is a rather high value for the circulatory blood volume of one lung.

CASE 3.—Right-sided pulmonectomy was undertaken because of bronchogenic carcinoma. Four hundred fifty c.c. of blood were given intravenously fifty minutes after the beginning of thoracotomy. Twenty-five minutes later, all the vessels and the main bronchus to the right lung

were occluded. The lung was then seen to be atelectatic. Twenty-nine minutes after the occlusion, the labelled blood was injected into the right pulmonary artery and blood samples were collected ten and fifteen minutes later. The vessels, but not the bronchus, were then released to the same lung. The lung, therefore, had a free circulation but still remained atelectatic. The specific activity, as shown in Fig. 3, decreased to a constant level from the twenty-second to the fortieth minute. The main bronchus to the right lung was then released and the lung expanded. At the same time the activity decreased even further.

The circulatory corpuscle volume and the total circulatory blood volume were calculated, first, during the period when both the vessels and the bronchus were clamped, and, second, after only the vessels had been released, and third, after the bronchus had also been freed. As illustrated in Fig. 3, the total circulatory blood volume during the first stage of operation when both the vessels and the bronchus were occluded amounted to 3,870 cubic centimeters. It increased to 4,100 c.c. when only the vessels were freed, and to 4,640 c.c. when the bronchus also was released. Consequently, when only the circulation to the right lung, which was partially atelectatic, was released, the circulating blood volume to that lung amounted to 4.9 per cent of the total circulatory blood volume. When the bronchus to that lung also was freed, some stored blood in the right lung must have been thrown into the circulation, since the activity continued to decrease. The calculated circulatory blood volume of the right lung then amounted to 16.6 per cent of the total circulating blood volume.



Weight 94 kg
Haemoglobin 60 %
Haematocrit 49%, 52 %
Red bl corpuscles 38 mill

I

Red blood corpuscles	2050 gr	22 gr/kg	1900 ml	20 ml/kg
Plasma	2020 »	21 s »	1970 »	21 »
Circulat blood volume	4070 »	43 s »	3870 »	41 »

II

Red blood corpuscles	2300 gr	24 s gr/kg	2130 ml	22 s ml/kg
Plasma	2020 »	21 s »	1970 »	21 »
Circulat blood volume	4320 »	46 »	4100 »	43 s »

III

Red blood corpuscles	2600 gr	28 gr/kg	2410 ml	25 s ml/kg
Plasma	2280 »	24 »	2230 »	24 »
Circulat blood volume	4880 »	52 »	4640 »	49 s »

Fig. 3.—Case 3. Determination of the circulating blood volume of one lung. See text.

From these results it apparently may be concluded that blood is stored in an atelectatic lung when the ventilation is either bad or obstructed. The working of this mechanism is difficult to explain. It may be assumed that the arteriovenous anastomoses open during bad ventilation, and that the capillaries to certain parts of the lung are stored with unaerated blood.

In Case 1 the circulatory blood volume of one lung amounted to 14.3 per cent of the total circulatory blood volume, in Case 2 to 20 per cent, and in Case 3 to 16.6 per cent. The mean value of these determinations in three patients indicate that the circulatory blood volume of one lung is as much as 17 per cent of the total circulatory blood volume.

Determination of Circulatory Blood Volume of Part of Lower Limbs.—

CASE 4.—This patient, a man, was being treated for duodenal ulcer. In the morning the patient was placed in a recumbent position and blood pressure cuffs were applied to the lower limbs. The pressure in the cuffs was elevated above the blood pressure of the lower limbs for

twelve minutes. Immediately after starting the occlusion of the circulation to the lower limbs, the tagged erythrocytes were injected intravenously. Samples of blood were measured with regard to their activity at the fifth to the twelfth minute after the injection. A constant level was obtained. The circulation was then released to the legs. The result was dilution in the activity of the blood. Equilibrium was soon established and a constant level was present in the samples of blood taken from the twenty-fifth to the sixtieth minute after injection. The values of the specific activity of the samples of blood are shown in Fig. 4. The circulating blood volume was calculated during the period of occlusion of the circulation to the lower limbs and was found to be 3,805 cubic centimeters. After deflation of the cuffs, it increased to 4,405 cubic centimeters. The calculated circulatory blood volume to a part of the lower limbs amounted, therefore, to 600 c.c., or 13.6 per cent of the total circulatory blood volume.

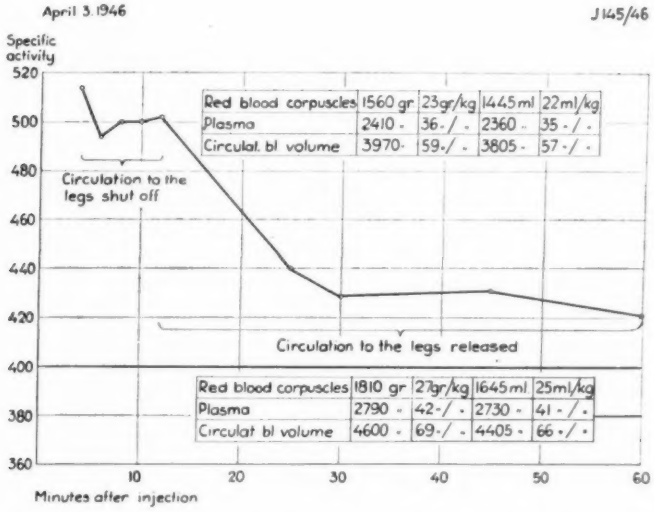

April 3. 1946
J 145/46
Specific activity
520
500
480
460
440
420
400
380
360
Red blood corpuscles 1560 gr 23gr/kg 1445 ml 22ml/kg
Plasma 2410 - 36 - / - 2360 - 35 - / -
Circulat. bl volume 3970 - 59 - / - 3805 - 57 - / -
Circulation to the legs shut off
Circulation to the legs released
Red blood corpuscles 1810 gr 27gr/kg 1645 ml 25ml/kg
Plasma 2790 - 42 - / - 2730 - 41 - / -
Circulat bl volume 4600 - 69 - / - 4405 - 66 - / -
10
20
30
40
50
60
Minutes after injection

Fig. 4.—Case 4. Determination of circulating blood volume of the lower limbs. See text.

SUMMARY

1. The fact that injected tagged erythrocytes maintain a constant level of activity in the circulation up to a minimum of one hour after the injection has made it possible to study certain unsettled circulatory problems.

2. The circulatory blood volume of one lung during pulmonectomy has been determined by means of tagged erythrocytes in three patients. The mean value of the circulatory blood volume through one lung has been shown to be 17 per cent of the total circulating blood volume.

3. The circulatory blood volume of the lower limbs has been determined and found to be 13.6 per cent of the total circulating blood volume.

I am greatly indebted to Clarence Crafoord, Head Surgeon of the Surgical Chest Clinic, who has afforded me facilities for carrying out these investigations in the course of operation.

I also wish to express my sincere thanks to The Board of Swedish Medical Research for the grants bestowed in connection with this investigation.

I beg to extend my warm thanks to Professor G. de Hevesy, for his unfailing interest, and to Professor Manne Siegbahn, who kindly placed radioactive phosphorus at my disposal.

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INTRUSION OF AORTIC ROOT INTO MITRAL ORIFICE IN HYPERTENSIVE DISEASE; RADIOLOGIC OBSERVATIONS ON LIVING PERSONS

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RECENT experience[1,2] gained in radiologic studies of calcified intracardial structures shows that not only the mitral annulus fibrosus is recognizable, but also adjacent calcified areas of the "fibrous skeleton"[3,6] of the heart, such as the fibrous trigona (central fibrous bodies) and the aortic ring with its supporting fibers. If these structures are calcified they can be identified easily, and the position, spatial interrelationship, and movements can be studied in living persons. Using the proper technique,[1,2] the frequency of radiologic demonstration of intracardial calcifications gradually approaches their pathoanatomic incidence. This amounts to 7 (5 to 10 per cent) in one hundred patients of all ages and to 20 per cent in those after the fifth decade.[4,5] This estimation, however, includes also minute calcifications, the visualization of which in living persons is not practicable with the present facilities.

The configuration of the normal mitral ostium is generally considered as being ellipsoid with occasional slight flattening of the anteromedial aspect. The degree and extent of the flattening is not specified in anatomic descriptions at our disposal. The mitral annulus fibrosus does not completely encircle the mitral ostium. It is a horseshoe-shaped part of the ellipsoid, situated on the posterior, lateral, and anterior aspects of the ostium. The medial portions are not surrounded by the fibrous annulus. In this area the posterolateral section of the aortic ring and its supporting fibers, contiguous portions of the trigona, and fila coronaria[3,6] form the mitral ring. Fig. 1 shows the anatomic appearance of the mitral orifice after the removal of the auricles. The typical roentgen appearance of the calcified mitral annulus fibrosus with no calcifications in the constituent posterolateral section of the aortic ring is illustrated in Fig. 2. The calcification is horseshoe-shaped, like the annulus itself. The ring is incomplete. With progress of calcareous deposit the aortic ring also may become involved. In such instances both structures together form a rigid, continuous calcified circle or ellipsoid around the mitral orifice, as seen in Fig. 3.

From the anatomic view of the atrioventricular ostia also can be seen the close proximity of the root of the aorta and the mitral orifice. This explains that pathologic variations in the size and shape of the aortic root might in-

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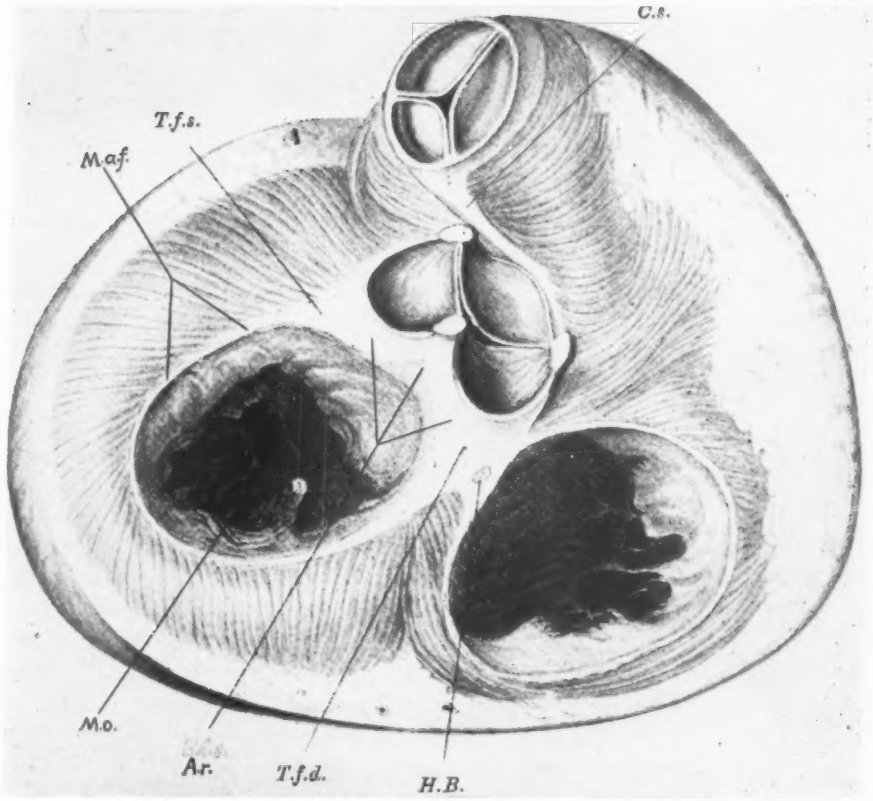

Fig. 1.—View of the fibrous skeleton of the heart and of anatomic relationship of aorta and mitral ostium after removal of the auricles. *M.o.*, mitral ostium; *M.a.f.*, mitral annulus fibrosus; *A.r.*, aortic ring; *T.f.s.*, left fibrous trigonum; *T.f.d.*, right fibrous trigonum; *C.s.*, tendon of pulmonal conus; and *H.B.*, bundle of His. (After Tandler, J.: Anatomie des Herzens, Jena, 1913, Gustav Fischer.)

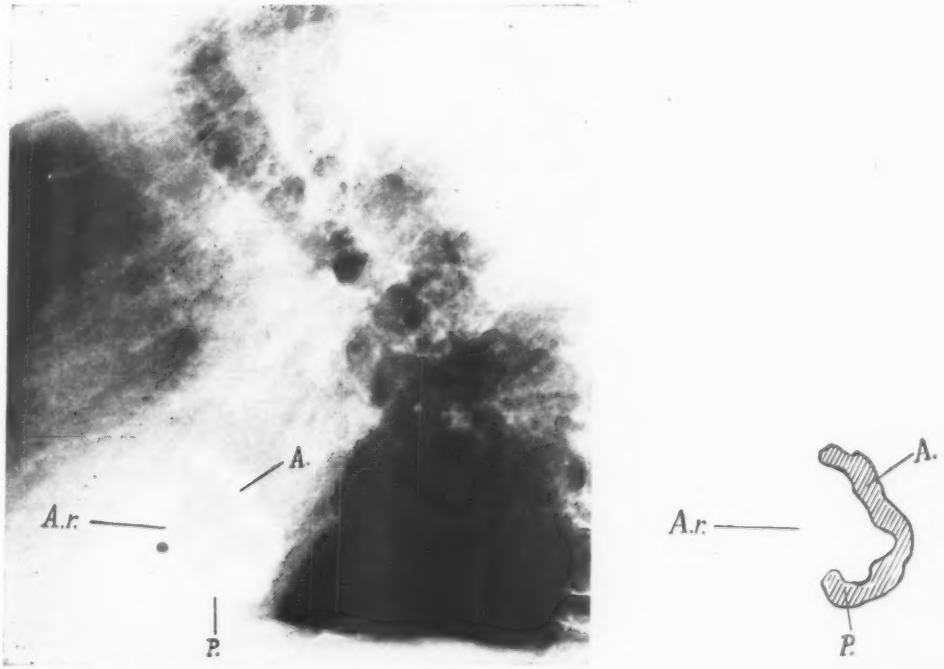

Fig. 2.—Radiographic view (left lateral) of calcified mitral annulus fibrosus with no calcifications in aortic ring (75-year-old woman with no hypertension and no cardiac symptoms). The calcium shadow is J-shaped. *P.*, posterior branch of annulus fibrosus; *A.*, anterior branch; and *A.r.*, region of the non-calcified aortic ring.

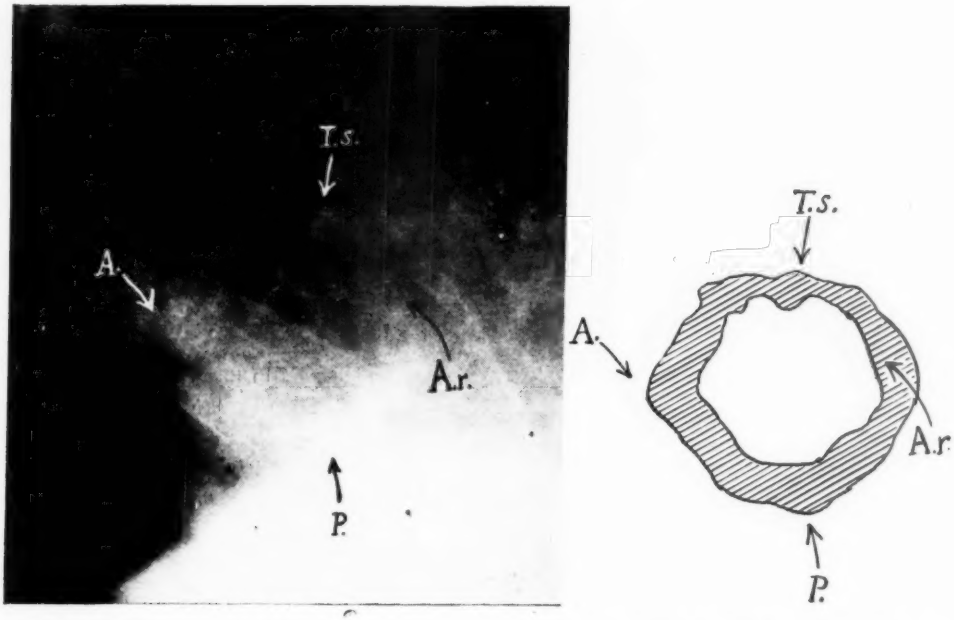

Fig. 3.—Radiographic view (right oblique) of calcified mitral annulus fibrosus with calcareous deposits in parts of the aortic ring. An 82-year-old man with compensated arteriosclerotic heart disease but no hypertension. Long, blowing diastolic murmur of aortic insufficiency. The calcium shadow is circular. *P.*, posterior branch of the annulus fibrosus; *A.*, anterior branch; *A.r.*, calcareous deposits in aortic ring; and *T. s.*, area of the left fibrous trigonum.

Fig. 4.—View of anatomic relationship of aorta and mitral ostium after removal of the auricles in a case of arteriosclerotic dilatation of the aorta. *M.o.*, mitral ostium; *A.*, aorta; *A.r.*, aortic ring; and *M.a.f.*, mitral annulus fibrosus. Note slight flattening of the orifice at the root of the aorta (*A.r.*). An 83-year-old man with generalized arteriosclerosis and mild hypertensive disease (blood pressure 180/100).

fluence the shape of the mitral ostium. A heart specimen in a case of arteriosclerotic dilatation of the aorta, prepared by us after removal of the auricles, shows flattening of the anteromedial portion of the mitral orifice (Fig. 4). This distortion is due to the mitral orifice adapting its shape to the expansion of the dilated aorta, which may be less marked on the specimen than it was in the lifetime of the patient, when hydrodynamic influences contributed to the widening of the aorta.

In a group of eighty-five cases of radiologically observed intracardiac calcifications, sixteen showed a completely calcified ring around the mitral ostium. In thirteen of these cases the composite calcium shadow of the annulus fibrosus and of the aortic ring was circular or ellipsoid. In three cases it was not circular, but crescentic. The greater, or posterolateral arc of the crescent, was identified as the calcified annulus fibrosus, and the lesser, or anteromedial arc, as the calcified posterolateral section of the aortic ring. These arcs were joined in the region of the calcified fibrous trigona. The rigidity and the unity of the crescentic-shaped rings were likewise noted. Deformity persisted uniformly in diastole and systole during several months of observation.

In Case 1, the appearance of the ostium is similar to that demonstrated in the specimen showing dilatation of the aorta. It is flattened on the anterolateral aspect of the ellipsoid (Fig. 5). Case 2 illustrates more advanced intrusion of the aorta, causing considerable loss of the surface of the orifice (Figs. 6 and 7). The appearance of the mitral ostium in Case 3 (Fig. 8), concerning the relationship of the annulus fibrosus to the aortic root, is similar to the foregoing observation. The amounts of lime deposit are less in this instance.

COMMENT

The radiologic demonstration was only practicable because there were extensive calcifications of both the mitral annulus fibrosus and of the aortic ring, a somewhat rare coincidence. However, protrusion of the aortic root into the mitral ostium may often take place in hypertensive disease, even though the absence of calcification prevents radiologic demonstration. The calcification itself seems not to contribute to the encroachment, only to its radiologic demonstrability. A figure of Giese,[6] showing a radiograph of a section of the heart cut in the plane of the mitral orifice and of the adjacent part of the aortic root, illustrates such an occurrence. The mitral annulus fibrosus is calcified. The noncalcified aortic ring intrudes into the mitral orifice (Fig. 9). The author makes no note of the deformity or of the disease afflicting the patient.

A diastolic murmur was heard at the apex in each of our three cases. Whether or not this was caused by stenosis of the mitral ostium following the intrusion of the aortic root cannot be decided from these studies. Clinical and electrocardiographic investigations with sound tracings have been carried out recently along these lines by Rytand.[7] His studies included our Cases 1 and 2 in which complete A-V block was present. According to his observations the murmur seems to follow auricular systole and is not caused by narrowing of the mitral orifice.

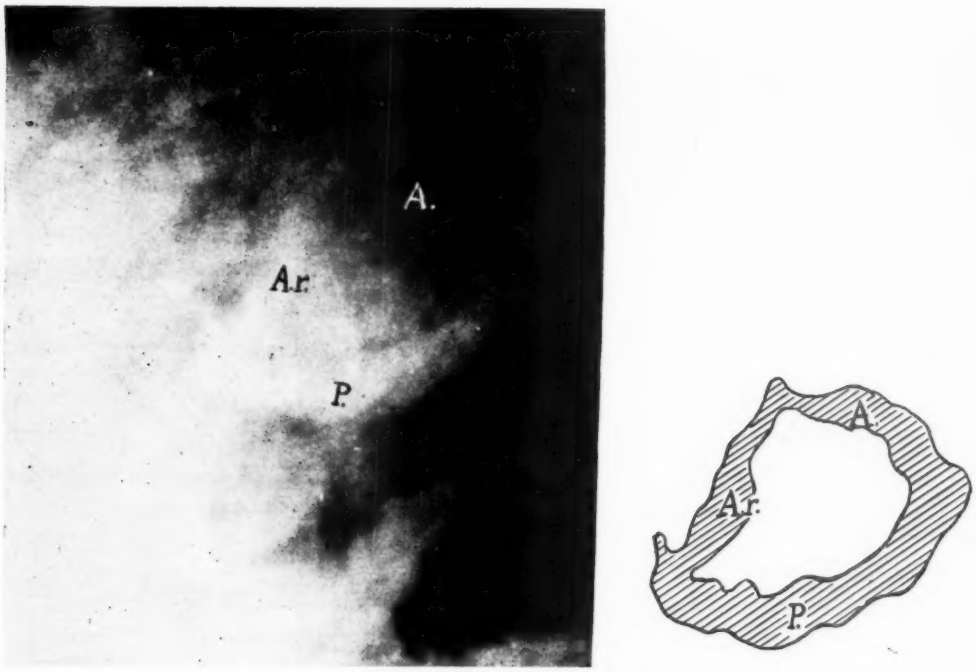

Fig. 5.—Radiographic view (left posterior oblique) of the calcified mitral annulus fibrosus and of parts of aortic ring in a case of hypertensive disease. Note considerable flattening of the mitral orifice in area of the aortic root. *P.*, posterior branch of the mitral annulus fibrosus; *A.*, anterior branch; and *A.r.*, calcareous deposits in the aortic ring. A 79-year-old woman, with moderate hypertension (blood pressure 200/90), dyspnea, coarse systolic murmur. Auricular activity during ventricular diastole (complete A-V block).

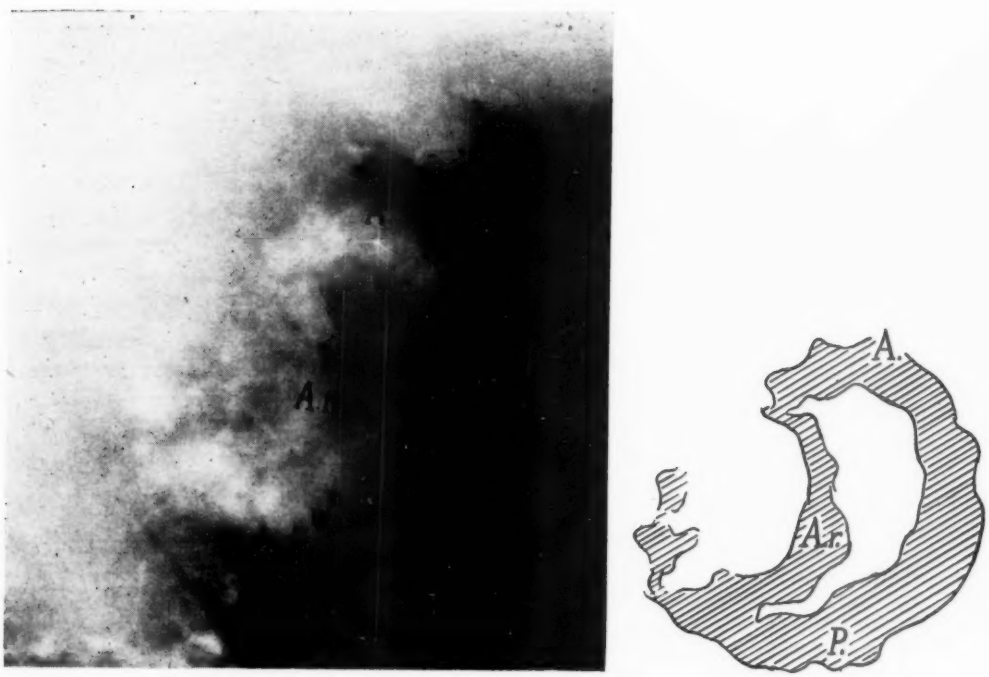

Fig. 6.—Radiographic view (left posterior oblique) of the calcified mitral annulus fibrosus and of a section of the aortic ring with intrusion of the aortic root into the mitral orifice. *P.*, posterior branch of the mitral annulus fibrosus; *A.*, anterior branch; *A.r.*, calcareous deposits in bulging (posterolateral) section of aortic ring. Calcifications in left lateral area are located in the membranaceous septum (proved by autopsy). A 72-year-old woman with advanced hypertensive disease (blood pressure 270/110), congestive failure, systolic murmur and thrill, and blowing diastolic murmur at apex, with auricular activity during ventricular diastole (complete A-V block).

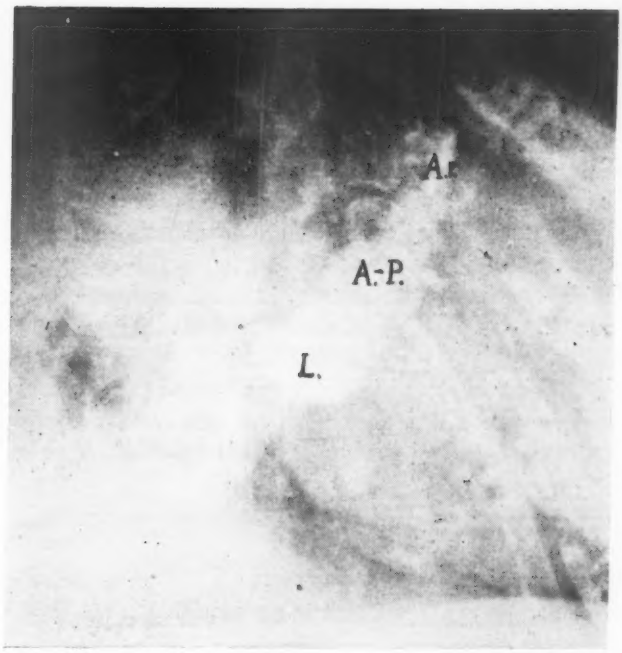

Fig. 7.—Radiographic view (right anterior oblique) of same case illustrated in Fig. 6, showing that calcifications of the mitral annulus fibrosus and of the aortic ring are in the same plane. *L.*, lateral portions of the calcified mitral ring; *A.-P.*, anterior and posterior branches of the annulus fibrosus overlying each other in this projection; and *A.r.*, bulging calcified aortic ring in the plane of the fibrosus annulus.

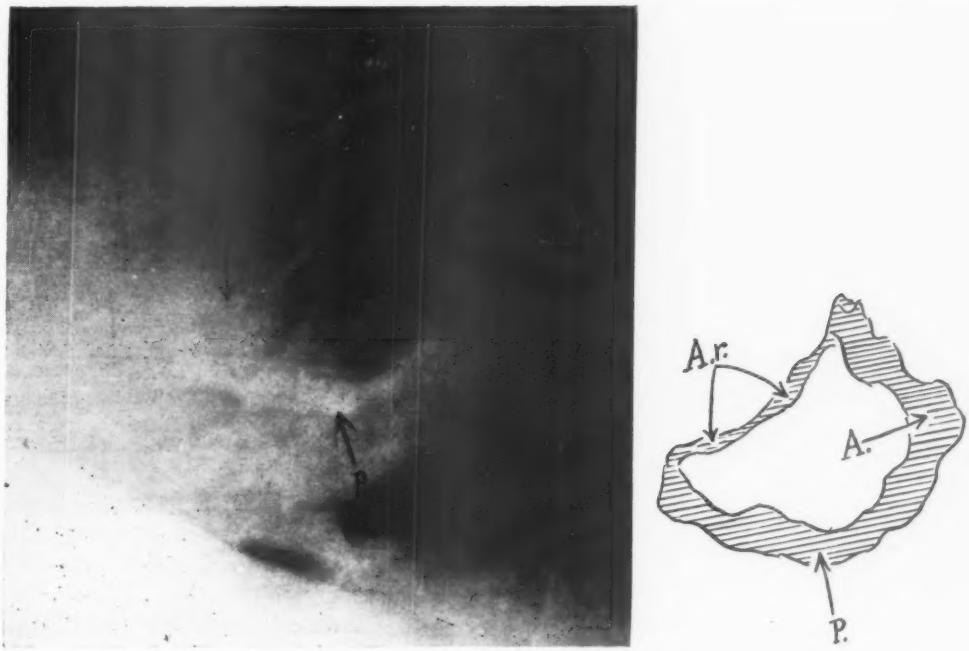

Fig. 8.—Radiographic view of the calcified mitral annulus fibrosus and of the posterolateral section of the aortic ring, bulging into the mitral orifice. *A.*, anterior branch; *P.*, posterior branch of the calcified mitral ring; and *A.r.*, calcifications in the protruding aortic ring. A 73-year-old woman with advanced hypertensive disease (blood pressure 230/105), diastolic and harsh systolic murmur. Sinus rhythm. Congestive failure, compensated.

In the same way the possibility of functional changes may be considered in the light of these findings. The narrowing of the mitral orifice must be very pronounced before it produces a significant mechanical obstacle to the circulation. Allan[8] found that a loss of 75 per cent of the cross section of the mitral ostium reduces the inflow to the ventricle a little, and that this reduction is easily overcome by a rise of the blood pressure. In our observations the loss of the cross-section area has not reached such a degree. Assuming that the shape of the mitral orifice was, prior to the deformity, ellipsoid, and the aortic root was circular, the surface loss was estimated on the radiographs, in Case 1, as being 35 to 40 per cent, in Case 2, 50 to 55 per cent, and in Case 3, 60 to 65 per cent. It also has to be considered that the shape and size of the mitral annulus fibrosus is correlated more to the condition of the left auricle than to that of the mitral valves.[9]

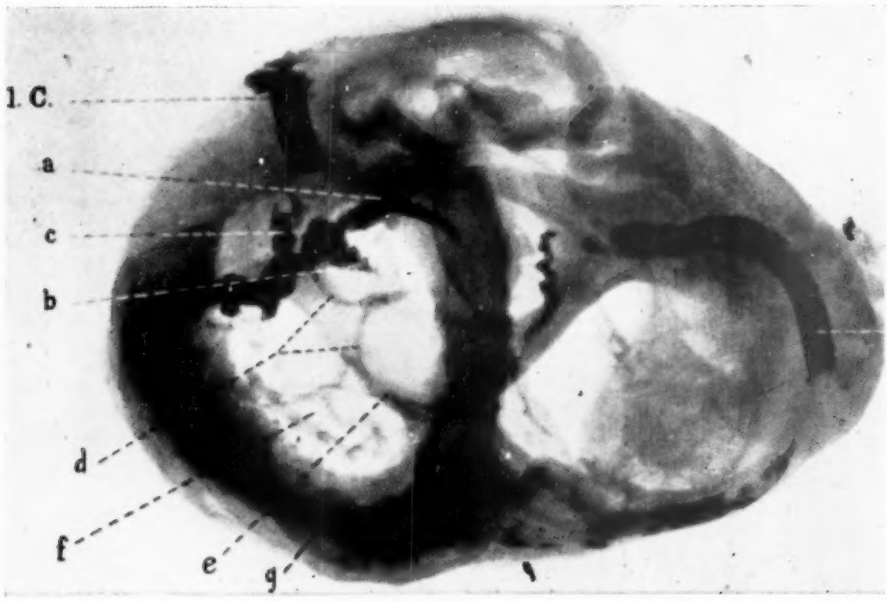

Fig. 9.—Radiograph of a heart specimen cut through the mitral ostium to the plane of the atrioventricular ostia. *l.C.*, calcified left coronary artery; *a.*, extension of calcifications into the interventricular septum; *b.*, extension of calcifications into the aortic leaflet; *c.*, extension of calcifications into anterior portions of the myocardium; *d.*, soft tissue shadow of the noncalcified left and posterior semilunar valves of the aorta; *e.*, soft tissue shadow of the aortic ring bulging into the mitral ostium; *f.*, mitral ostium deformed by protruding aortic root; and *g.*, calcifications in the posterior branch of the mitral annulus fibrosus. (From Giese, W.: Verkalkungen des Herzskelettes, Bietr. z. path. Anat. u. z. allg. Path., 1932.)

In cases of rigid calcifications, like those we have described, interference may be expected with the physiologic systolic reduction in the circumference of the mitral orifice. This rigidity may favor regurgitation by hindering the proper diminishing of the orifice into a narrow slit by the systolic contraction. Whether or not, in a noncalcified condition of the mitral ring, protrusion of the aorta into the mitral ostium contributes to the completeness of the systolic closure and counteracts the effects of functional dilatation of the orifice is one of the problems that remains to be solved.

Changes in the anatomic interrelationship of intracardiac structures in pathologic conditions are well known. Intrusion of the interventricular septum into the right ventricle in cases of cardiac hypertrophy[10] or intrusion of the interauricular septum into the lumen of the right auricle in cases of left auricular dilatation[11] have often been observed. Gager[12] recorded a case of hypertensive disease in which a dissecting aneurysm of the root of the aorta encroached on the mitral ostium. In this case a loud diastolic murmur was heard. Narrowing of the mitral orifice by intrusion of the aortic root, according to available information, is not described. Its anatomic demonstration would require special autopsy technique; namely, removal of the auricles, as seen on our Figs. 1 and 4, prior to the conventional opening of the heart. Its radiologic demonstration is based on the presence of calcifications, proper fluoroscopic and radiographic technique, and analysis of the findings along the lines suggested in this article.

SUMMARY

1. Fundamentals for the radiologic demonstration of anatomic relationship of the root of the aorta to the mitral ostium in living persons, in the presence of intracardial annular calcifications, are described.

2. Three cases of hypertensive disease are presented, in which the radiologic examination showed that the root of the aorta intruded into the mitral ostium and caused loss of the cross-section area of the orifice.

3. There is indication that the aortic root may encroach on the mitral orifice also in cases of hypertensive disease, in which absence of calcifications does not permit the radiologic demonstration of these structures.

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CONGENITAL SINGLE CORONARY ARTERY IN MAN

Report of Nine New Cases, One Having Thrombosis With Right Ventricular and Atrial (Auricular) Infarction

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ABSENCE of one of the two main coronary arteries, with the entire heart being supplied by a congenital single coronary artery, is one of the rarest of reported cardiac anomalies that may have some practical clinical significance. Only twenty-two cases have been found in the literature, and we here report nine additional cases which we have collected. In only one of the previously reported cases were thrombosis and occlusion of the branches of the single coronary artery present with myocardial infarction of the anterior apical left ventricle; while among our adult cases there were three with myocardial infarction.

Myocardial infarction in the right ventricle is very rare, except for involvement of the small portion adjacent to an infarcted area in the left ventricle. In our Case 1 there was the association, heretofore unreported, of infarction of the posterior wall of the right ventricle and right atrium with thrombosis in the branches of a single coronary artery (the right) in a patient whose left coronary artery was absent. Electrocardiographic abnormalities could be correlated with the localization of the atrial and ventricular infarction.

Cases 1 and 2 came under our observation at Gallinger Municipal Hospital during the past year. A survey of the autopsy records of this hospital during the last five years brought to light Case 3. Six other cases (Cases 4 through 9) were found by searching the autopsy records of congenital cardiac anomalies at the Army Institute of Pathology.*

CASE REPORTS

Case 1 (Hospital No. B97778).—A 62-year-old white man was admitted to Gallinger Municipal Hospital on Nov. 21, 1944, at 11:15 A.M. He complained of agonizing pain behind the sternum, most severe just to the right of the sternum in the fourth intercostal space. The pain, which had begun shortly after the patient had eaten some cooked ham earlier in the morning, was

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described as "a choking sensation," "cutting off my breath," and was obviously intense. He felt as though vomiting would relieve the pain. On admission to the hospital the pain was said to radiate into both arms, but this radiation was not described to other examiners a short while later. He said that he had not had similar episodes of pain, angina, hypertension, or heart disease. However, his wife said that several years previously he had had a similar but milder episode of pain in the chest. An operation for "gallstones" had been performed in 1927. No other history could be obtained.

Physical examination was limited by the acute distress and critical state of the patient. He was moderately obese; the skin was ashen grey, cold, and moist. He moaned constantly. The pulse was weak, thready, and slow, with a rate of 39 per minute. Respiration was shallow and labored, with a rate of 20 per minute. The pupils were not constricted. The lungs were free of abnormality on examination. The cardiac impulse could not be seen or felt. The left cardiac border was percussed in the anterior axillary line in the fifth intercostal space. The heart sounds were very faint or distant. There were no murmurs. The rate of the heart beat was 39 per minute, with occasional irregularities suggesting extrasystoles. The blood pressure, which had been 160/100 in the admitting office, had declined to 94/52 by the time he reached the ward. The rectal temperature was 97.6° Fahrenheit.

The urine on admission had a specific gravity of 1.020, a 3 plus reaction to the test for albumin, and three to six white cells per high power field. The blood count was as follows: hemoglobin, 15 Gm. per 100 c.c. of blood; red blood cells, 4,340,000 per c.mm.; white blood cells, 14,000 per c.mm.; differential, 75 per cent neutrophiles, 4 per cent transitional cells, 19 per cent lymphocytes, 1 per cent large mononuclear cells, and 1 per cent basophiles.

The diagnosis of coronary arterial occlusion with posterior basal myocardial infarction was made and appeared to be confirmed by several electrocardiograms. He was treated with morphine, atropine, and oxygen nasally. On the day after admission he developed paralysis of the left side of the body and became completely anuric despite catheterization. On the second day after admission his rectal temperature rose to 100° F., he became cyanotic and less responsive, and numerous fine, high-pitched, musical and sibilant expiratory râles were heard throughout both sides of his chest. Left ventricular cardiac failure and possible bronchopneumonia were suspected, but before treatment for either of these complications was started, he died.

Electrocardiographic records (all properly standardized) were made on five occasions during his three days in the hospital. They were quite unique. (1) A tracing made at 11:50 A.M. on Nov. 21, 1944 (Fig. 1) showed a ventricular rate of 40 and an atrial rate of approximately 400 per minute. There was complete atrioventricular dissociation with the onset of atrial fibrillation during the recording of Lead I. Despite the changing atrial mechanism, little alteration of ventricular rhythm occurred. The R-T interval was 0.52 second. The QRS intervals were 0.10 to 0.12 second. In Lead I, the Q wave was absent, the R and S waves were equal, the S-T segment was greatly depressed (6 mm.) below the isoelectric line and sloped gradually downward from its low take-off, and the T wave was diphasic, reaching only 1 mm. above the isoelectric line in its last portion. In Lead II, a shallow Q wave (1 mm.) was present, the R wave was slurred on its descending side, and the S wave was absent. The R-T segment was broadly convex with its take-off 5 mm. above the isoelectric line. The T wave was not distinct from the R-T segment. In Lead III, the Q wave was 3 mm. in depth, the R wave again slurred on its downstroke, and the R-T segment greatly elevated with its take-off 9 mm. above the isoelectric line. The coved segment sloped upward and was continuous with the T wave, which sloped gradually down to the isoelectric line.

(2) A tracing (Fig. 2, *A*), taken ten minutes later with multiple precordial leads, showed essentially the same abnormalities in the three standard leads. Q waves were absent in each of the precordial leads. As the exploring electrode was moved across the chest from right to left, several important changes occurred. The R wave increased steadily in height from 1 mm. in CF_1 to more than 23 mm. in CF_5 and went off the record in CF_6. The S wave increased in depth from 11 mm. in CF_1 to 16 mm. in CF_6. Both R and S waves were slurred in each lead. The S-T take-off was depressed in each and the depth of this depression increased steadily from 2 mm. in CF_1 to 11 mm. in CF_6. The S-T segment sloped upward in Leads CF_1 through CF_5,

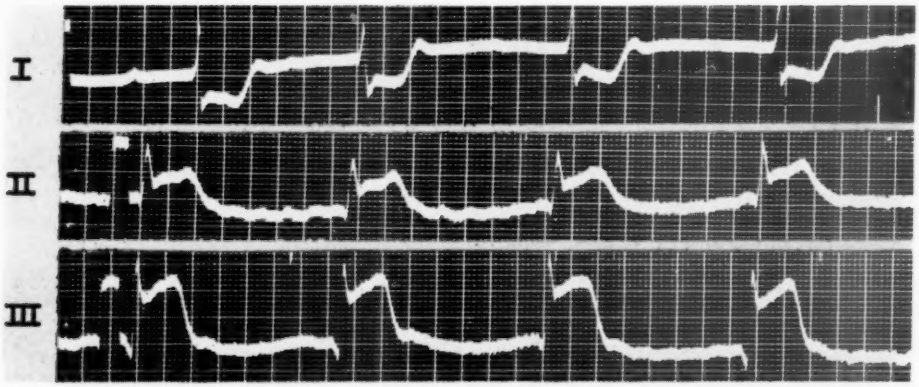

Fig. 1.—Electrocardiogram of Case 1, taken three hours after the onset of pain. Atrioventricular dissociation, with atrial fibrillation or flutter at times. See text for descriptions.

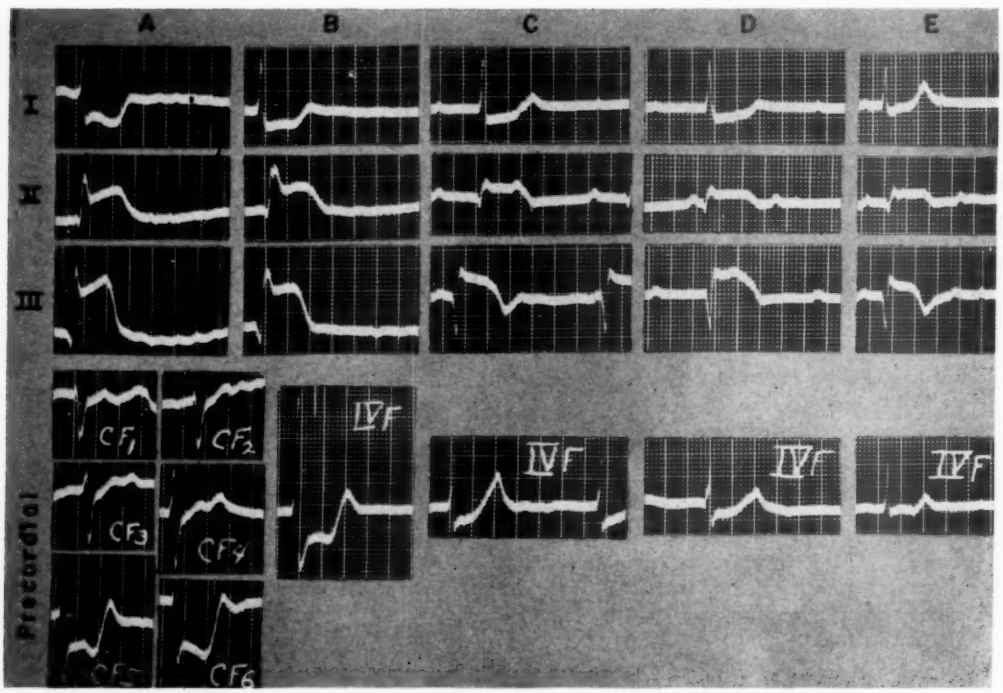

Fig. 2.—Electrocardiograms of Case 1, in sequence to emphasize rapid progress of Q_3-T_3 type changes, atrial rhythmic changes, and variations in P waves, *f* waves, and P-T_A contours. *A*, three hours and ten minutes after onset, atrial fibrillation, with notched *f* waves in Lead II. Note changes in the CF leads. *B*, five hours after onset. *C*, twenty-four hours after onset. *D*, thirty-one hours after onset; note atrial T waves. *E*, fifty-one and one-half hours after onset, with elevation of P-T_A segment in Lead II. See text for description.

but in CF_6 slanted downward from the take-off. The T waves appeared to be diphasic and of low voltage in CF_1 through CF_3, but they were obscured somewhat by the atrial deflections. In Leads CF_4 through CF_6 the T wave was diphasic, with the initial limb downward. The amplitude of T, especially of the initial inverted segment, became steadily increased with the increase in depression of the S-T segment.

(3) A tracing (Fig. 2, *B*) was made at 2:00 P.M. of the same day, or about two hours after the first record. The abnormalities differed only slightly from those in the previous tracings. In Lead I, the R wave was slightly higher, the S-T segment was less depressed (4 mm.) and was horizontal with a slight upward convexity instead of being sloping. In Lead II, the R wave was broadly slurred and deeply notched at its apex, the S-T segment was horizontal instead of slanting and was 5 mm. above the isoelectric line. In Lead III, the R wave was more broadly slurred, the S-T segment was again horizontal instead of slanting and was 8 mm. above the isoelectric line. Only one precordial lead was made, IVF, which may have been made with a misplaced exploring electrode because it closely resembled the previous CF_5.

(4) Another tracing was obtained on Nov. 22, 1944, at 9:30 A.M., (Fig. 2, *C*). There was atrioventricular dissociation with an auricular rate of 80 and a ventricular rate of 55 per minute. P_1 and P_2 were upright, P_3 was bifid, and P_4, isoelectric. In Lead I the R wave was 10 mm. high, there being no Q waves. The take-off of the S-T segment was depressed by 2.5 mm., and sloped upward to a prominent, upright T wave. In Lead II there was a Q wave of 1 mm., with low, slurred R wave, and no S wave. The R-T segment was elevated 2 mm., and descended to an inverted T wave. In Lead III, there was a deep (9 mm.) Q wave, slurred R wave, elevated (4.5 mm.) R-T segment which sloped downward with upward convexity to an inverted, coved T wave. Lead IVF had a slurred S wave (5 mm.); the S-T segment was depressed (4 mm.) and sloped upward, and the T wave was high and peaked.

(5) Another tracing (Fig. 2, *D*) was taken at 4:00 P.M. of the same day, and was essentially similar to the previous one except for decreased amplitude of the T waves. "Atrial" T waves were seen clearly at times, with variation in the $P\text{-}T_A$ interval.

(6) A sixth tracing (Fig. 2, *E*) was taken on Nov. 23, 1944, at 12:30 P.M., approximately fourteen hours before death. The atrioventricular dissociation persisted with a ventricular rate of 50 per minute. The P waves were unchanged. In Lead I, the S-T segment was less depressed than previously (1 mm.), and sloped upward, with upward convexity, to a prominent, upright T wave. In Lead II, the Q wave was 1 mm. in depth, the R wave was low (3 mm.) and markedly slurred. The R-T segment was elevated (2 mm.), and the T wave was inverted, with a high take-off. Lead III had a deep Q wave (6 mm.), with a slurred low R wave, an elevated R-T segment (3 mm.), and an inverted T wave. In Lead IVF, there was a small (1 mm.) S wave, the S-T segment was only slightly depressed (0.5 mm.), and the T wave was upright. Atrial $P\text{-}T_A$ segments were elevated in Lead II.

Necropsy: The heart (Fig. 3) had the usual general shape and position. The pericardial cavity contained about 10 c.c. of clear yellowish fluid. In the epicardium over the entire right ventricle there were numerous small subepicardial hemorrhages. A reddish purple, mottled discoloration with softening and thickening was present over the posterior surface and acute margin of the right ventricle and over the lower posterior part of the right atrium. After removal and opening, the heart weighted 410 grams. The wall of the left ventricle was thickened, being about 25 mm. in its middle portion. The papillary muscles were moderately enlarged. The wall of the right ventricle was thickened, being about 15 mm. in the region of the purplish discloration. This area, which was very soft, congested, edematous, and hemorrhagic, represented a recent myocardial infarction. The anterior apical portion of the left ventricle was somewhat lighter in color than usual and cut with slightly increased difficulty, suggesting the presence of fibrosis. The left auricular appendage was filled with firm, dark red clot which was adherent to the wall. The valves presented no abnormalities. Above the right anterior* aortic sinus of Valsalva there was the ostium (5 mm. in diameter) of the single coronary artery. Low in the left anterior aortic sinus of Valsalva was a minute shallow dimple (2 mm. in diameter and 1 mm. in depth) which

*BNA nomenclature.

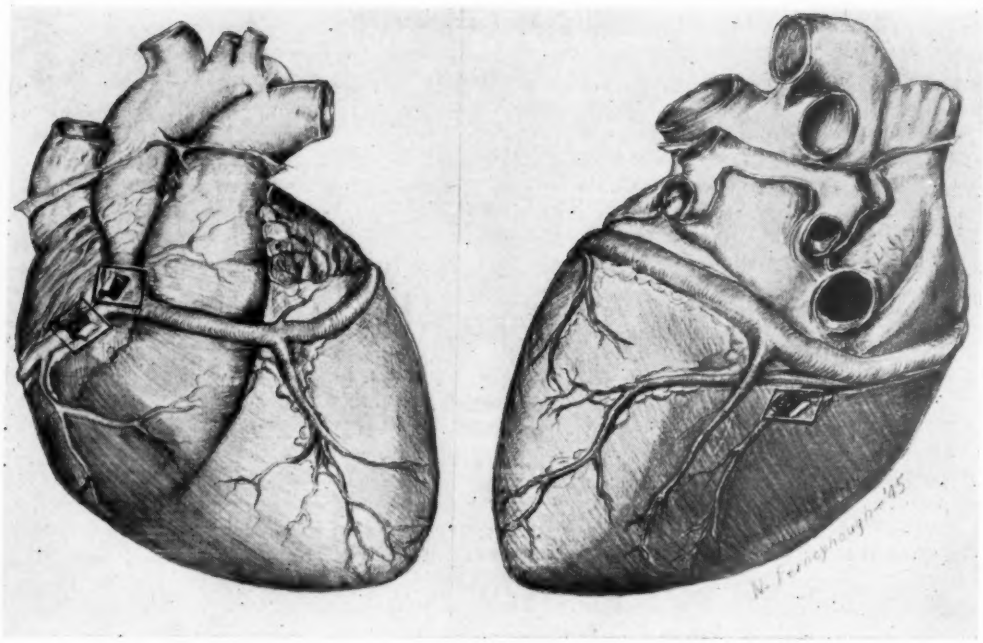

Fig. 3.—Artist's conception of the heart of Case 1, anterior and posterior views. Boxed areas indicate sites of thrombosis in the branches of the single coronary artery. Heavily shaded areas represent the infarcted portions of the right ventricle and atrium.

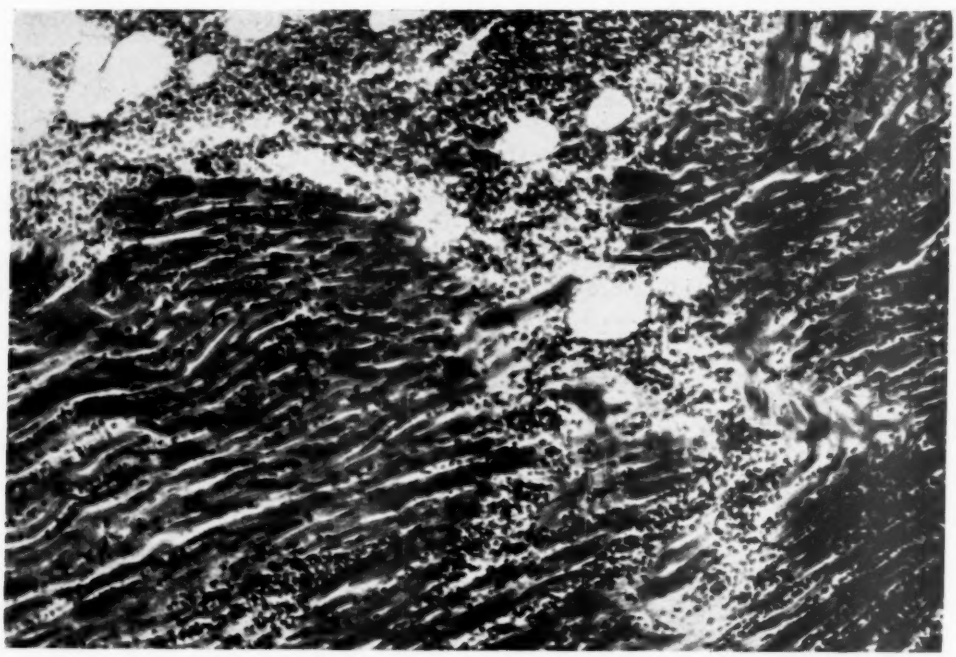

Fig. 4.—Case 1. Right ventricular infarction, recent, hemorrhagic phase; section from the acute margin of the heart. x 230. (Photograph by the Army Institute of Pathology.)

on careful study was found not to be connected with any vessel. No additional openings of coronary arteries were found on close inspection of the aorta and pulmonary arteries.

A single large coronary artery was found to supply the entire heart. The coronary artery coursed anteriorly to the right between the pulmonary artery and right auricular appendage. About 1 cm. from its origin this vessel divided into two large branches, as follows: (1) A large artery which followed the course of the usual right coronary artery in the right atrioventricular sulcus to reach the posterior surface of the heart and terminate in the posterior interventricular sulcus. From this vessel several smaller branches arose in the usual positions to supply the front and back of the right atrium and ventricle. (2) An anomalous large artery which passed across the front of the conus region to assume the position of the circumflex branch of the usual left coronary artery. From this artery three important branches arose: (a) a small vessel in the position of the usual anterior descending artery (about 1 mm. in external diameter); (b) a very minute arterial twig which ran upward between the pulmonary artery and left auricular appendage to terminate just before it reached the usual site of origin of the left coronary artery; (c) a large vessel which passed in the left atrioventricular sulcus in the position of the usual left circumflex artery and gave rise to branches of the usual size supplying the lateral and posterior part of the left ventricle and atrium. Terminal branches of this vessel anastamosed with the terminal twigs of the right branch of the single coronary artery.

After the coronary arteries were opened several points of occlusion or stenosis were found, as follows: (1) A large, firm and dark red thrombus at the point of bifurcation of the single main coronary artery. This thrombus occluded the point of origin of the right branch and partly occluded the origin of the large anomalous branch which passed in front of the conus. The thrombus was firmly adherent to the endothelium which at that place was reddened, slightly elevated, and appeared to be the site of a subintimal hemorrhage. (2) A firm, dark red thrombus which almost completely occluded the lumen of the right main branch of the coronary artery midway

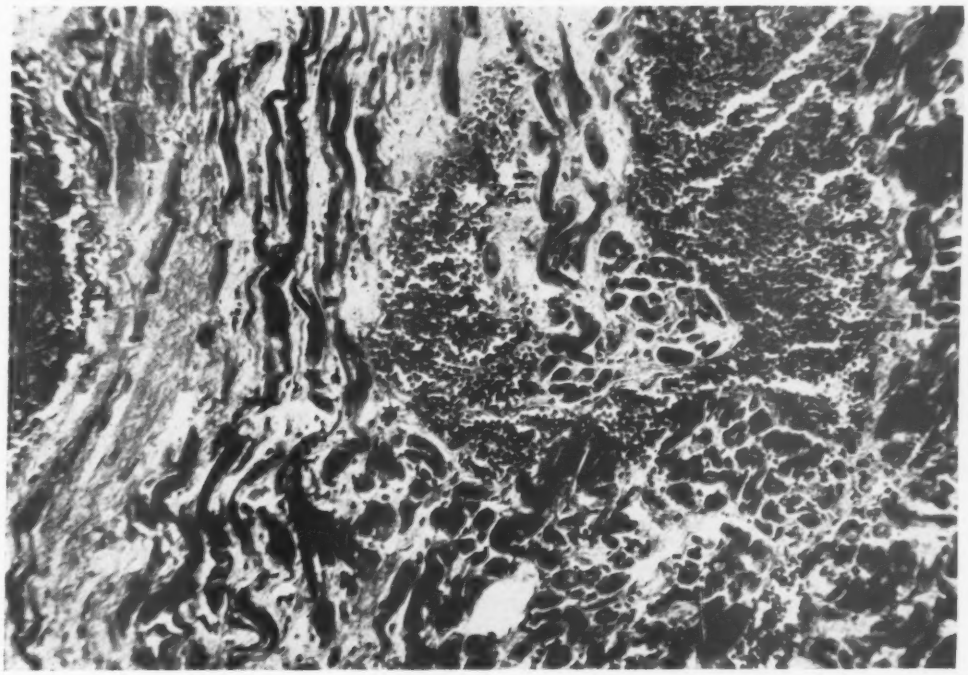

Fig. 5.—Case 1. Section from the posterior wall of the right ventricle. x 230. (Photograph by the Army Institute of Pathology.)

between its origin from the single large trunk and the acute margin of the heart. (3) A firm, dark red thrombus which completely occluded the lumen of a medium-sized branch arising from the right branch of the coronary artery just before the origin of its terminal branch in the posterior interventricular sulcus. (4) An almost complete occlusion of the thread-sized lumen of the anterior descending artery by atheromatous plaques. The coronary arteries in general were thickened and stiffened with numerous atheromatous plaques throughout their course, except for the portion in front of the region of the conus. No abnormalities of the coronary veins were found.

Sections through the recent infarction of the acute margin (Fig. 4) of the right ventricle and through the posterior surface of the right ventricle (Fig. 5) and atrium (Fig. 6) showed marked

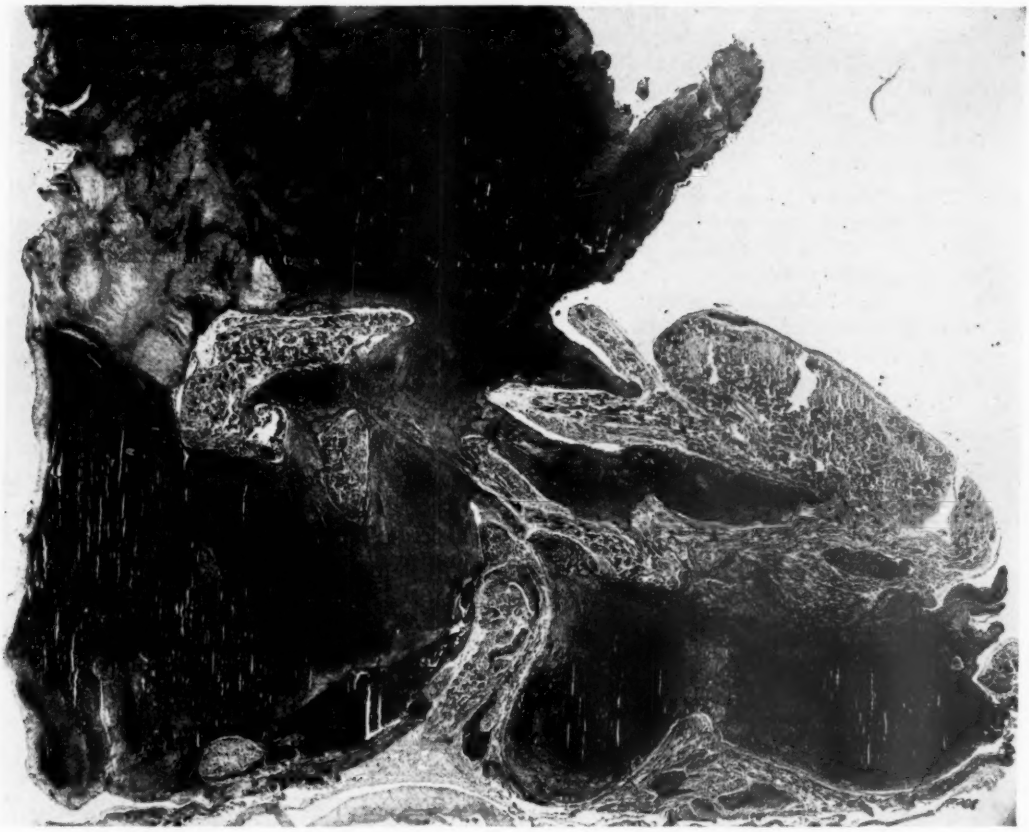

Fig. 6.—Case 1. Right atrial infarction, recent, hemorrhagic phase; section from the posterior wall of the right atrium. x 16. (Photograph by the Army Institute of Pathology.)

swelling of the myocardial fibers, loss of normal structure, and marked differences in staining quality of the fibers. In some of these areas the myocardial fibers were much paler than usual, and the fibers were granular and fragmented. In some areas the fibers were stained darker than usual with loss of both transverse and longitudinal striations and with varying degrees of nuclear degeneration. The myocardial fibers throughout most of these sections were separated widely by masses of erythrocytes, with many polymorphonuclear and lymphocytic leucocytes. Scattered throughout these sections were occasional broad bands of fibrous connective tissue. The endocardium and epicardium in these sections were thickened, with swelling and distortion of the endothelial and mesothelial cells, disintegration of the loose fibrous connective tissue, inter-

stitial edema, and patchy extravasation of blood cells. In several places well-organized mural thrombi were seen beneath the trabeculae cordis. The myocardial fibers in the regions of these thrombi were completely distorted or had almost completely lost their structure and were separated by very marked extravasation of blood. Most of the capillaries throughout these sections were distended with blood cells. Some of the smaller branches of the coronary arteries in these sections were occluded by thrombi.

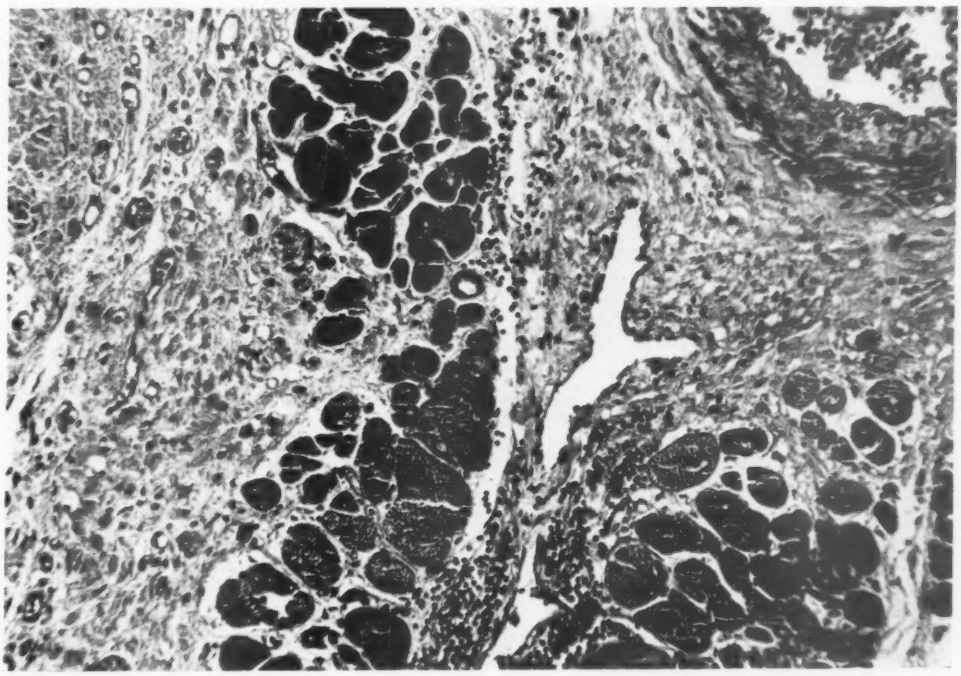

Fig. 7.—Case 1. Myocardial fibrosis; section from the anterior middle region of the left ventricle. x 230. (Photograph by the Army Institute of Pathology.)

The sections through the anterior and middle wall of the left ventricle (Fig. 7) revealed some shrinking of the myocardial fibers with proliferation of the interstitial connective tissue.

The two lungs weighed 875 grams, were poorly aerated, bluish grey in color, and firmer than usual. Pale, watery, frothy fluid oozed freely from the cut surfaces. In the lower lobes, especially on the left side, there were numerous reddish granular areas from which yellow purulent fluid could be expressed. The bronchi revealed only slight infection of the mucosa. The pulmonary vessels were not unusual. Sections of the lungs showed engorgement of the capillaries. The alveoli were filled with clear fluid, "heart failure cells," red blood cells, white blood cells, and debris in varying proportions.

The liver extended 6 cm. below the right costal margin and weighed 1,500 grams. Its capsule was smooth and pale brown. Slicing revealed a typical nutmeg appearance. There was marked congestion with dilation of the central veins, engorgement of the portal areas, and extravasation of erythrocytes. The gall bladder was absent. The two kidneys weighed 325 grams and had prominent fetal lobulation. The capsules stripped with difficulty, leaving a finely granular surface. The left adrenal was somewhat thickened and contained a cystic cavity filled with about 3 c.c. of brown fluid. Examination of other organs revealed no significant variations from normal. Permission to examine the central nervous system was withheld. The anatomic diagnosis was: Congenital anomaly of coronary arteries, thrombosis of the right branch of the single

coronary artery, infarction of the myocardium of the acute margin of the right ventricle and the posterior portion of the right ventricle and atrium, moderate hypertrophy of left ventricle, arteriolonephrosclerosis, pulmonary edema, bilateral basal bronchopneumonia, passive congestion of the liver, and old healed scar of cholecystectomy.

CASE 2 (Hospital No. C12465).—A 42-year-old Negro laborer, was admitted to Gallinger Municipal Hospital on Aug. 21, 1945, because of prolonged and progressive weakness due to advanced pulmonary tuberculosis, and died eight days later. There were no symptoms or findings suggesting cardiac disease.

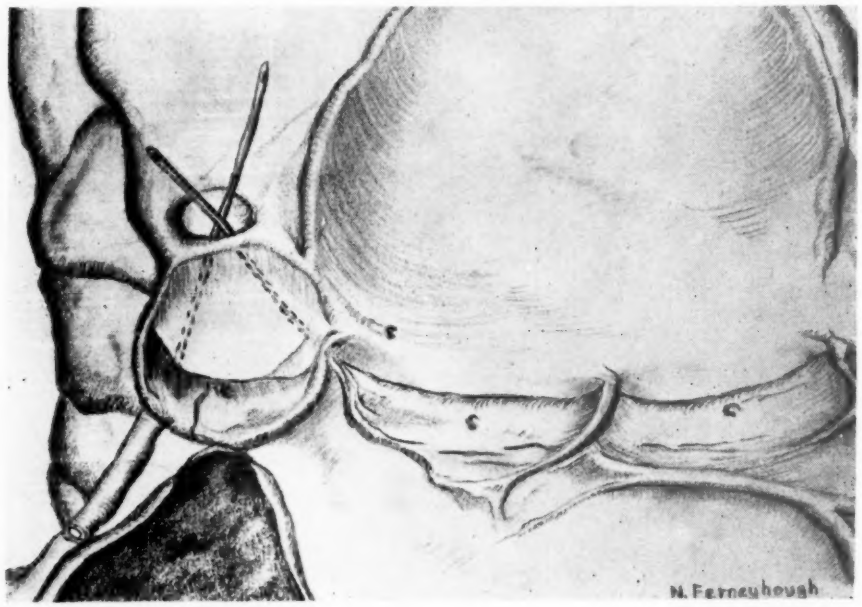

Fig. 8.—Case 2. Drawing of the single coronary artery ostium, with two needles inserted to indicate the course of the left and right main branches.

Autopsy revealed pulmonary tuberculosis, lobar pneumonia, loculated hydrothorax, thickened pleura, and fatty liver. There was only a single coronary ostium 8 mm. in diameter in the left anterior aortic sinus near the anterior commissure (Fig. 8). Five millimeters beyond the ostium, the artery divided into two branches, 4 mm. and 2 mm. in diameter. The larger branch had the usual distribution of the left coronary artery and the smaller, that of the right coronary artery. There was no evidence of another coronary arterial ostium or of any other abnormality of the heart. Several discrete atheromatous plaques were seen in the ascending aorta.

CASE 3 (Hospital P44182).—A 38-year-old Negro woman entered Gallinger Municipal Hospital on Dec. 19, 1941, with chest pain and vomiting of eleven to twelve hours' duration. She had had several previous episodes of substernal pain and dyspnea, at times associated with vomiting. The blood pressure was not obtainable, the pulse rate was 100 per minute. Short systolic murmurs were heard at the apex and tricuspid area. In spite of the administration of oxygen, morphine, and aminophyllin, the patient died thirteen hours after admission. This patient was not seen by either of us. The record was found by Dr. B. A. Fitzgerald, during an analysis of all autopsies at Gallinger Municipal Hospital in the past five years.

According to the record, "The heart weighed 300 grams. The myocardium did not appear thickened and was of good color. The aortic valve was bicuspid but not otherwise remarkable. Only the orifice of the right coronary could be detected; the left could not be found. However,

section through the myocardium showed a very small but apparently adequate coronary circulation." Microscopic examination revealed "considerable subintimal hyalinization and thrombosis in all states of organization, some areas which show swelling of the fibers, with loss of outline, and precipitation of cell constituents. In other areas this condition has progressed and there is degeneration of fibers with polymorphonuclear infiltration. In other places there is fresh scar tissue." There was microscopic evidence of syphilitic aortitis, with adventitial thickening, medial scarring, and perivascular round cell infiltration; passive congestion of lungs, liver, spleen, and kidneys; and benign adenoma of the liver.

CASE 4 (Army Medical Museum 44956).—A 46-year-old Negro soldier had had several previous hospital admissions in the ten months before his death with a diagnosis of "chronic myocarditis with cardiac decompensation." Electrocardiograms had shown progressive left axis deviation, delay of intraventricular conduction, and abnormal T waves. Before death he presented the usual picture of congestive heart failure. At autopsy he was found to have diffuse arteriosclerosis, chronic congestion of all organs, hypostatic pneumonia, and left frontal and occipital infarcts. At the tip of the left ventricle there was a large area which was only 4 mm. in thickness. The lower half of the lateral wall of the left ventricle was covered by a massive mural thrombus, and beneath this the myocardium was pale, translucent, and degenerated. There was no left coronary orifice and the whole blood supply of the heart came from the right coronary artery. The lumen of the right coronary artery as it passed around the base of the right ventricle was markedly enlarged. The left anterior descending branch was large and showed only a moderate amount of sclerosis without constriction of the lumen. Beginning at the right coronary orifice, coursing downward and anteriorly through the base of the interventricular septum, and emptying into the anterior descending branch 4 cm. below the atrioventricular groove, there was an artery carrying the main left coronary blood supply. The left circumflex branch was medium-sized and patent. The terminal portion of the right circumflex was small. The interventricular septum just below the undefended space was pale and bloodless.

CASE 5 (Army Medical Museum 96957).—A 22-year-old white soldier died suddenly after a rapid hike. Abnormal findings at the autopsy were limited to the heart. The right heart was markedly dilated and distended with a large amount of blood. The myocardium showed no evidence of degeneration or infarction. The left coronary orifice and coronary artery were patent throughout their entire length. There was no orifice for the right coronary artery except a blind pouch, which did not lead into the right coronary artery.

CASE 6 (Army Medical Museum 106062).*—A 37-year-old white soldier had had episodes of mild substernal pains at monthly intervals for two years before death. The terminal episode consisted of the usual picture of acute coronary occlusion. The electrocardiogram showed left axis deviation with elevated S-T segments in Leads I and II and inverted T_3. Autopsy disclosed hemopericardium. There was no evidence of myocardial rupture. The aortic valve was bicuspid. An aneurysm was present which opened by an oval aperture 3 mm. below the posterior aortic cusp, and it was believed that the rupture of this aneurysm had caused the hemopericardium and death. A single coronary orifice arose from the sinus of the posterior cusp. There was immediate division of the artery into the right and left coronary arteries; these vessels showed minimal atherosclerosis, and no coronary occlusion was found.

CASE 7 (Army Medical Museum 139328).—A 35-year-old white soldier complained of severe substernal pain coming on after breakfast, associated with transient loss of consciousness. He had had two previous attacks seven and five years prior to admission. The blood pressure was 92/75, and on the next day a pericardial friction rub could be heard, together with râles in the left base. On the day after admission the patient sat up in bed and suddenly fell to the floor, dead. Autopsy disclosed a large dissecting aneurysm involving the ascending and descending aorta. The aortic valve was bicuspid, and the anterior cusp was thickened, calcified, and contracted. The left coronary artery was normal in origin, branches, and distribution. The vessels were

*This case has been reported recently in another connection by L. S. Medalia and J. F. Drapiewski, AM. HEART J. 31:103, 1946.

patent throughout and free of sclerosis. At the site of the right coronary artery in the aorta there was an unperforated dimpling. The right side of the heart received its blood supply from a vessel which appeared to be a branch of the left circumflex coronary artery. This vessel, too, was patent and not sclerotic. The myocardium was of normal thickness.

CASE 8 (Army Medical Museum 100984).—A three-day-old white female infant, with no available history, presented multiple cardiac and extracardiac anomalies on autopsy, as follows: bicuspid aortic valve with a single coronary ostium in the right portion of the large posterior sinus of Valsalva; absence of the left coronary ostium which was represented only by a small dimple; interatrial and interventricular septal defects; anomalous arrangement of the aorta; cleft palate, harelip, talipes equinovarus, imperforate anus, accessory calcified spleens, anomalous duodenum, absence of the left kidney, ovary, and uterine tube, and paraventricular cerebral cysts. Death was attributed to atelectasis and bronchopneumonia.

CASE 9 (Army Medical Museum 100704).—A 7-day-old white male infant died of the following congenital anomalies: hypoplastic aorta, left atrium and ventricle, and mitral valve; a single coronary artery, the right, 3 mm. in diameter and patent throughout; a rudimentary dimple replacing the left coronary ostium; dilated foramen ovale; hypertrophic fetal endocarditis; patent urachus; marked fetal lobulation of kidneys; and atelectasis of the lungs.

DISCUSSION

Reports of thirty-one cases of single coronary artery are available for comparison.[1-19] Krumbhaar and Ehrich[1] classified fourteen cases of this type of coronary arterial anomaly into: (1) cases of absence of the right coronary artery; (2) cases of absence of the left coronary artery, including: (a) those in which the missing vessel was replaced by two branches of the right coronary artery, a septal branch, and one passing behind the aorta, and (b) those in which a septal branch only replaced the missing vessel; and (3) miscellaneous and unclassified cases of absent coronary arteries. Seven other cases of this anomaly have been found in the available literature and nine new cases are described in the present report. The salient features of these cases are indicated in Table I and Fig. 9. In these thirty-one cases the heart was nourished by a right coronary artery alone in seventeen cases, by a left coronary artery only in eleven cases; in the other three cases the identity of the single coronary artery cannot be determined from the description. The aortic sinus of Valsalva from which the single coronary artery arose was as follows: In ten cases the vessel arose from the right anterior sinus; in six, from the left anterior sinus; in seven, from the posterior sinus (which in two cases was one of a bicuspid valve); and in eight the sinus of origin was not mentioned. In seven of the cases there was a dimple and in one case a blind pouch at the usual site of origin of the missing coronary artery; five of these were instances of absence of the left coronary artery. One or both of the coronary arteries may arise from the pulmonary artery, but we have omitted such cases from this discussion.

One previously reported case and two of our cases had thrombosis of one or more branches of the single coronary artery, with infarction of the myocardium as a result. In one case myocardial "ischemia" was described. In another case there was periarterial fibrosis microscopically. In one of our cases there was myocardial fibrosis and scarring of an earlier infarction, with considerable subintimal hyalinization and microscopic thrombosis of the coronary arteries. Seventeen

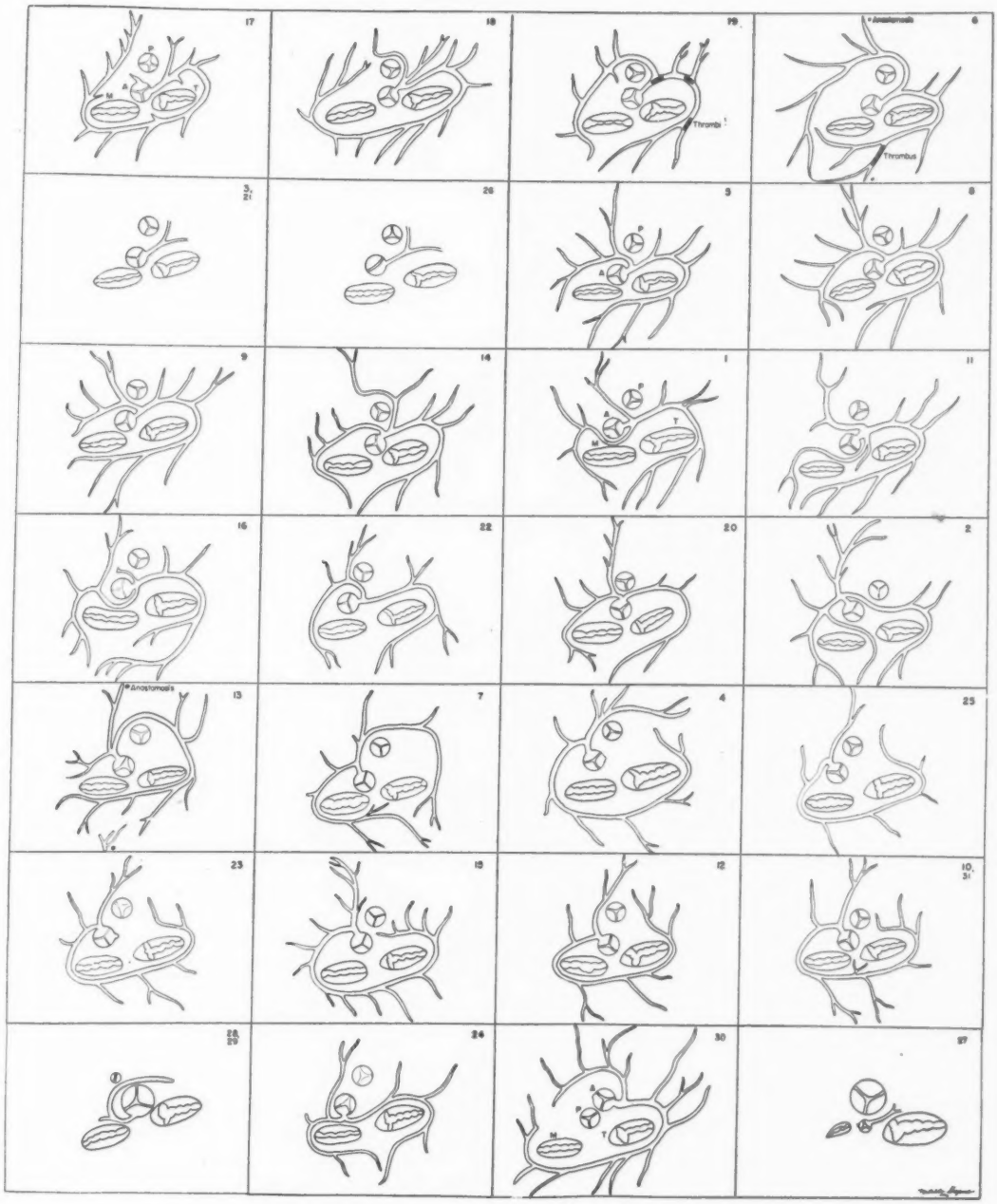

Fig. 9.—Diagrams of the pattern of the coronary arteries in the reported cases with a congenitally single coronary artery, constructed from available data. Numbered as in Table I. (Arranged in a sequence from a case with the single right artery encircling the heart, through intermediate grades of branched single arteries to a case with the single left artery encircling the heart. The cases without naming of the single artery or identification of a "posterior" sinus of origin and with other major anomalies are included.)

TABLE I. COMPARISON OF HEARTS WITH A CONGENITALLY SINGLE CORONARY ARTERY

CASE	AUTHOR, YEAR	AGE, SEX	CORONARY ARTERY PRESENT	SINUS OF ORIGIN	REMNANT OF ABSENT CORONARY ARTERY	THROMBUS	OTHER CARDIAC DISEASE OR ANOMALY	CAUSE OF DEATH
1	Bochdalek, 1867[2]	60-F	R	Right	—	—	Chronic mitral and aortic endocarditis	Chronic mitral and aortic endocarditis
2	Engelman, 1897[3]		L	?	—	—	—	Unstated
3	Garaud, 1909[4]	39-F	R	Posterior	—	—	Ischemia	Bronchitis, congestion, angina
4	Plaut, 1922[5]	37-M	L	?	Brown dimple in rt. sinus	—	Endocarditis lenta	Endocarditis lenta
5	Gallavardin and Ravault, 1925[6]	45-F	R	Rt. ant.	—	—	Chronic mitral and aortic endocarditis	Chronic mitral and aortic endocarditis
6	Smith and Graber, 1926[7]	46-M	R	?	—	Descending branch	Anat. and lat. infarct	Coronary occlusion, congestive heart failure
7	Petren, 1930[8]	33-M	L	Left	—	—	—	Apoplexy
8	Kintner, 1931[9]	65-M	R	Rt. ant.	—	—	—	Pneumonia, renal insufficiency (postoperative)
9	Born, 1933[10]	54-M	R	Rt. ant.	—	—	—	Empyema, gangrene of lung
10	Kochel, 1934-35[11]	39-F	L	Left	—	—	Early bicuspid endocarditis	Pneumonia, early bicuspid endocarditis
11	Sanes, 1937[12]	4-M	R	Rt. ant. (4 openings in common orifice)	Dimple ant. aortic sinus near commissure between cusps	—	Recent interstitial myocarditis	Acute glomerulonephritis, toxic myocarditis

12	Richter (Case I), 1937[13]	63-M	L	Left (higher than usual)	—	—	—	Cancer of stomach
13	Richter (Case II), 1937[13]	Adult	L	?	—	—	—	Unstated
14	Speer, 1938[14]	61-M	R	Rt. ant. ?	—	—	—	Cerebral hemorrhage
15	Krumbhaar and Ehrich, (Case I), 1938[1]	44-F	L	Left. ant.	—	—	Enlarged heart and chronic thickened mitral valve	Pulmonary embolism, thickened mitral valve
16	Krumbhaar and Ehrich (Case II), 1938[1]	35-F	R	Rt. ant.	—	—	Fine periarterial fibrosis	Cancer of uterus
17	Maddox and Isbister, 1940[15]	42-F	R	Posterior	Small branch running up between pulmonary artery and aorta, ending blindly	—	Acute rheumatic carditis. Quadricuspid pulm. valve. Anomalous rt. subclavian artery	Acute rheumatic carditis
18	King, 1940[16]	45-M	R	Rt. ant.	—	—	Left ventricle thickened and somewhat dilated	Lobar pneumonia
19	Roberts and Loube, Case 1	62-M	R	Rt. ant.	Dimple left ant. sinus. Minute artery twig between pulmonary artery and left auricular appendage	3	Myocardial infarction. Numerous atheromatous plaques in cor. arteries	Myocardial infarction, of right ventricle wall and right atrium. Congestive failure
20	Roberts and Loube, Case 2	42-M	L	Left ant.	—	—	—	Pulmonary tuberculosis, lobar pneumonia
21	Roberts and Loube, Case 3	38-F	R	?	—	Yes, microscopically	Myocardial infarction. Syphilitic aortitis, bicuspid aortic valve	Coronary occlusion, myocardial infarction
22	Roberts and Loube, Case 4	46-M	R	?	—	—	Myocardial infarction, apical, lateral	Congestive heart failure, myocardial infarction
23	Roberts and Loube, Case 5	22-M	L	Left	Blind pouch	—	Acute dilatation of rt. heart	Acute dilatation of rt. heart on unusual exertion

TABLE I. COMPARISON OF HEARTS WITH A CONGENITALLY SINGLE CORONARY ARTERY—(CONT'D)

CASE	AUTHOR, YEAR	AGE, SEX	CORONARY ARTERY PRESENT	SINUS OF ORIGIN	REMNANT OF ABSENT CORONARY ARTERY	THROMBUS	OTHER CARDIAC DISEASE OR ANOMALY	CAUSE OF DEATH
24	Roberts and Loube, Case 6	37-M	Divides into L and R.	Posterior	—	—	Bicuspid aortic valve, aneurysmal sac opening below posterior aortic cusp	Rupture of aneurysmal sac, hemopericardium
25	Roberts and Loube, Case 7	35-M	L	?	Unperforated dimpling at site of rt. cor. artery	—	Bicuspid aortic valve, anterior cusp thickened, calcified, contracted	Dissecting aneurysm
26	Roberts and Loube, Case 8	3-F	R	Posterior	Dimple	—	Bicuspid aortic valve, atrial and ventricular septal defects	Atelectasis bronchopneumonia. Multiple extracardiac anomalies
27	Roberts and Loube, Case 9	7-M	R	Rt. ant.	Dimple	—	Hypoplasia of left ventricle, mitral valve, atrium, aorta, dilated foramen ovale	Congenital heart disease, patent urachus, atelectasis
28	Monckeberg, Case I, 1924[17]	5-M	?	Posterior	—	—	Bicuspid pulmonary valve, tetralogy of Fallot	Unstated
29	Monckeberg, Case II, 1924[17]	—	?	Posterior	—	—	Same	Unstated
30	Ngai, 1935[18]	53-F	R	R. posterior	Dimple	—	Septal defects; transposition of aorta and pulmonary artery, rt. aortic arch, sinistroposition of rt. auricle	Atelectasis and pneumonia
31	Ravin and Geever, 1946[19]	—	L	?	—	—	—	"Extracardiac"

of the patients were males, nine were females, and the sex in the other two was not mentioned. The age of the twenty-six patients in whom this information was given ranged from 3 days to 68 years; on exclusion of the four children, the average age of these patients was 45 years. Four of the hearts had bicuspid aortic valves, and in one case there was a quadricuspid pulmonary valve. Six cases had other significant congenital cardiac anomalies.

Two of the hearts showed chronic mitral and aortic endocarditis; in one there was endocarditis lenta; and in another heart there was early endocarditis of a bicuspid aortic valve. One heart showed a "chronically thickened mitral valve," and in one of the instances of bicuspid aortic valve the anterior cusp was thickened, calcified, and contracted. In one heart there was recent interstitial myocarditis, and in one acute rheumatic carditis. In one of our cases there was acute dilatation of the right heart, with no other abnormality aside from the single coronary artery.

The cause of death in each of the cases was probably unrelated to the congenital anomaly of the coronary artery with the six following possible exceptions. In the case of Smith and Graber,[7] as in our Cases 1, 3, and 4, the anomalous coronary arteries may have prevented the utilization of anastomatic vessels to relieve the ischemia of the myocardium following thrombosis of the coronary arteries. Similarly, the angina and heart failure occurring in Garaud's[4] case may have been related to the ischemia observed histologically and might have been due to the lack of availability of compensatory anastamoses. However, the well-known frequency of myocardial ischemia and infarction in patients in the same age range as in these cases (38 to 62 years) diminishes the likelihood that the congenital anomaly alone was the main factor causing death. In our Case 5, the presence of acute dilatation of the right heart, associated with absence of the right coronary artery, suggests a possible casual relationship. In the other patients in this series who had some type of cardiac disease, such as endocarditis, other congenital cardiac anomalies, or rheumatic carditis, the congenital anomaly of the coronary arteries had no evident significance. In the other cases death was due to factors unrelated to the heart.

Case 1 of our series presented several unique features which were not present in any of the other cases. The infarction of the myocardium involved the larger portion of the wall of the right ventricle and a small portion of the atrium. An infarction of the right ventricle following occlusion of the coronary arteries is an extreme rarity[20] except in the small portion adjacent to the septum. This common observation has given rise to much speculation. Whitten[21] believed that the rarity of right ventricular infarction was related to anatomic differences in the angle with which the penetrating branches arose from the main coronary arteries in the two ventricles. He thought that the more obtuse angle with which the perforating branches arose in the right ventricle resulted in less sharp bending of these perforating arteries in the right ventricle, whereas the sharper angle of origin in the left ventricle gave rise to more traumatic bending during systole and predisposed to arterial degeneration. Others, since the time of Vieussens and Thebesius, have thought that the wall of the right ventricle was so thin that it might be adequately nourished by the so-called Thebesian, or luminal vessels,

whereas the wall of the left ventricle was so thick that only a thin portion next to the endocardium could be nourished by these channels. Some experimental basis for this belief has been established by Wearn[22] and Roberts.[23]

Recently Blumgart, Schlesinger, and Davis[24] called attention again to the importance of the intercoronary anastomoses as a source of blood supply for an area supplied by an occluded coronary artery. They found by studying careful injections that myocardial infarction might not occur following occlusion of one coronary artery until a subsequent stenosis or occlusion involved another coronary artery from which compensatory anastomoses had arisen. In our Case 1 this factor may have been very important in leading to the infarction, for the anterior descending coronary artery was already seriously stenosed by long-standing atheromatous changes and so could not serve as a source for supplying the myocardium normally nourished by the thrombosed right coronary artery. Furthermore, it seems quite likely that all the available intercoronary arterial anastomoses had been dilated greatly and utilized long before the coronary artery thrombosis occurred to compensate for the defect in distribution of the coronary arteries during early embryonic life.

In each of the four cases of myocardial infarction, and in each of the three instances of myocardial fibrosis or ischemia, the absent vessel was the left coronary artery. This finding may indicate that better compensation for an absent coronary artery is made when the single persisting vessel is the left coronary artery rather than in the converse situation. This supports a belief that an intact arterial supply is more essential for the thicker left ventricle than for the thin right ventricle.

Infarction of the auricular muscle has seldom been described. The same conditions exist in the thin auricular muscle which have been used to explain the rarity of right ventricular infarction. Since the experimental and clinical observations of Cushing, Feil, Stanton, and Wartman[25] it has become recognized that infarction of the auricle may occur and be suspected from electrocardiograms occasionally. The location of the atrial infarction in our Case 1 was very likely such as to involve the atrioventricular node and bundle also. Involvement of this specialized conduction tissue was probably the mechanism producing the complete atrioventricular block and dissociation which was recorded electrocardiographically. Careful correlation of the electrocardiographic and anatomic abnormalities of this case makes it appear to be a close analogy to experimental conditions where atrioventricular block is produced prior to injury of atrial or auricular muscle. Miller and Perelman[26] recently (since our case has been described in abstract[27]) have discussed somewhat similar electrocardiographic abnormalities in a patient on whom an autopsy was not performed. In the light of these earlier studies, our Case 1 seems to establish the following signs as grounds for suspecting future atrial infarctions: (1) atrial arrhythmias, especially if changing rapidly in type; (2) atrioventricular block; (3) changing contour of P or *f* waves; (4) changing contour of the P-T_A segment or interval and of the atrial T wave (T_A), if evident, as it may be with dissociation or prolonged P-R intervals. Precordial records, especially of the CF_1 or CF_2 positions or esophageal leads, might be expected to yield more information on this point

in suitable patients. Additional experimental and clinical studies on this important problem would be of interest. The atrial arrhythmia which varied from tachycardia to flutter and fibrillation was probably due to the ischemia of the atrial muscle, as were the changes in the atrial T waves, in *f* or P-wave contour, and P-T_A segments and intervals.

Another unique feature of this case was the presence of a probable subintimal hemorrhage at a point of thrombosis of the single coronary artery. Such lesions have been emphasized by Wartman,[28] Paterson,[29] Winternitz and coworkers,[30] and others as the basis for coronary thrombosis in some cases. Although the sections through this area were lost, gross inspection indicated the probability of subintimal hemorrhage.

The serial electrocardiograms obtained during the terminal illness of our first patient were quite unusual. We have been unable to find any report of exactly similar records. The magnitude of the deflection of the S-T segments was much greater than in any case of posterior basal myocardial infarction known to us. The use of multiple precordial leads made these records of even more value. The mode of death of this patient was readily explained as being due to acute congestive heart failure after loss of function of much myocardial tissue, pulmonary edema, terminal bronchopneumonia, and cerebral arterial occlusion by an embolus arising from the mural thrombus.

Our second case showed no evidence of coexisting cardiac disease, death being due to an entirely unrelated illness, and well exemplifies the possible compatibility of this anomaly with normal existence.

Although it cannot be established except by speculation, the possible mechanisms by which anomalies of the coronary arteries arise, as in these cases, are as follows: (1) absence of the anlage for one coronary artery; (2) a displacement of the anlage of one coronary artery so that it fuses with the anlage of the other; or (3) occlusion by thrombosis, infection, or maldevelopment of one coronary artery soon after its formation, with failure of subsequent canalization and with compensatory dilatation of the remaining vessels. In our Case 1 it seems most probable that the third mechanism occurred. In this case there is good reason to believe: (1) that the coronary arteries originally arose with a normal pattern, and (2) that soon afterward occlusion of the trunk of the left coronary artery occurred with subsequent degeneration of the connection between the tiny dimple at the site of the usual left coronary ostium and the tiny threadlike artery arising from the anomalous vessel in front of the conus and running upward between the pulmonary artery and left auricle. (3) As a result of this, the usually minute vessels connecting the right and left coronary arteries in front of the conus became dilated to form the anomalous large branch arising from the single coronary artery. This mechanism might similarly be invoked in the case of Maddox and Isbister,[15] who described a small branch running up between the pulmonary artery and the aorta, which they believed was the remnant of the origin of the normal left coronary artery. In their case, however, no aortic dimple was described. Because, according to this speculation, the intercoronary anastomoses had been dilated since early embryonic life, there was less possibility for com-

pensatory dilatation of anastomoses to occur after the occurrence of coronary thrombosis.

A displacement of the anlage of the "missing" coronary artery would seem to be the most common mechanism. Our Case 2, in which the common trunk divided 5 mm. beyond the ostium into two branches corresponding to the right and left coronary arteries, might represent a displacement of the anlage to a point just beyond the origin of the "single" coronary artery. Kintner's[9] case is representative of a group of cases in which the "absent" left coronary artery is replaced by a branch of the right coronary artery which passes to the left between the aorta and pulmonary artery and passes through the septum to the anterior surface. Kintner,[9] Sanes,[12] and Speer[14] refer to the abnormality in their cases as "anomalous origin of the left coronary artery" rather than as "absent coronary artery" and, in a sense, rightly so.

Brown[31] states that the anlagen of the coronary arteries appear about the fourteenth day of fetal life, the left being formed before the right, and that they appear in the truncus arteriosus before that structure is divided by the spiral septum. An aberration in the site of division by the septum might account for anomalous origin of one or both coronary arteries from the pulmonary artery; twenty-one such cases have been reported, according to Soloff.[32] It is conceivable that a dorsal deviation of the septum, which is formed from the lateral cushions of the truncus arteriosus, could crowd the anlage of the left coronary artery toward the right so that the two anlagen fused. After the subsequent counter-clockwise rotation of the dividing truncus arteriosus, the anomalous left branch of the fused anlagen might pass between aorta and pulmonary artery, and penetrate the septum. Similarly, inclusion of an unusually large part, or all, of the right lateral cushion into the ventral (or pulmonary artery) division of the truncus arteriosus might result in a bicuspid aortic valve, which occurred in three cases, or a quadricuspid pulmonary valve, which was observed in one case.

Hyrtl[33] has stated that to identify this type of anomaly as a true case of absent coronary artery it must be proved that the single artery present really supplies the entire heart. By only the first of the above named mechanisms could this postulate be fulfilled, namely, by an absent coronary arterial anlage.

The group of cases exemplified by that of Petren[8] and the first case of Krumbhaar and Ehrich,[1] in which the right coronary artery was absent (the right heart being supplied by a continuation of the circumflex branch of the left coronary artery) would seem to conform to the Hyrtl postulate, in that one artery apparently supplies the whole heart. Similar cases are those of Kochel[11] and of Richter,[13] and our Case 7. In Plaut's[5] case the right heart was supplied by a large branch from the anterior descending branch of the left coronary artery, but the small brown dimple in the aorta at the usual site of the right coronary ostium may have represented an anlage which had failed to develop. Since, in the larger proportion of the cases, this is not the mode of substitution for the missing coronary artery, we feel that Hyrtl's postulate need not determine the identification of cases with only one coronary artery, and that this group of

anomalies should be identified as the origin of the coronary arterial circulation from a single trunk rather than as a true congenital absence of one coronary artery.

SUMMARY

Nine new cases of absence of a coronary artery are added to twenty-two previously reported cases of this anomaly. Three of these nine patients had occlusion at one or more points of the single coronary artery, with resultant myocardial infarction.

One patient had massive infarction of the right ventricle and auricle, and a unique series of electrocardiograms was recorded. These indicate that atrial infarction should be suspected with the occurrence of: (1) atrial arrhythmias, especially if changing rapidly in type; (2) atrioventricular block; (3) changing contour of P or *f* waves; (4) changing contour of the P-T_A segment or interval and of the atrial T wave (T_A) if evident, as it may be with dissociation or prolonged P-R intervals.

The embryologic and clinical features of the anomaly are discussed and mechanisms for its production are propounded. This anomaly is compatible with normal cardiac function, but adds extra hazard in the presence of coronary artery disease because the available collateral anastomoses must be utilized early in life.

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A METHOD OF DETERMINING THE EFFECTIVE THERAPEUTIC LEVEL IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN

A Preliminary Report

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IN THE course of studies on the effective treatment of subacute bacterial endocarditis with penicillin over the past two years at this hospital, it was felt that there was need of some definite basis for determining adequate therapy for each specific infectious organism involved. A careful study of the literature demonstrated the universally empiric character of therapy and the lack of any objective criterion. The methods in general use all depend on indirect comparisons. The penicillin sensitivity of the organism is determined directly, but the blood level of penicillin during therapy is assayed by means of some "standard" organism. From these two measurements, continued therapy is planned so that a blood level as high or higher than the indicated sensitivity is maintained. This method has given, and is continuing to give, therapeutically satisfactory results in patients with highly sensitive organisms. In patients with more resistant organisms it has not been demonstrated that this is the proper approach.

It occurred to us that a more satisfactory method of outlining adequate therapy in cases with resistant organisms might be based on the action of a patient's own serum, during penicillin administration, upon the specific infectious organism isolated. As far as can be determined, such an approach to the problem has not been made. With this in mind, we have been selecting patients with comparatively resistant cases, in whom the organism has required 5 or more Oxford units of penicillin per cubic centimeter of culture medium to inhibit growth completely for eighteen hours, for closer study. Our findings seemed sufficiently promising to warrant this preliminary note.

After starting intensive therapy in the patients selected, adequate blood samples are drawn, preferably five minutes before the time of injection when the intermittent (intramuscular) method is employed, to permit making the usual

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TABLE I

PATIENT	ORGANISM FOUND	DATE	STANDARD TURBIDITY METHODS		GROWTH OF OWN ORGANISM IN OWN SERUM				RATIO OF SERUM PENICILLIN CONCENTRATION TO SENSITIVITY			
			SENSITIVITY OXFORD UNITS	SERUM LEVEL OXFORD UNITS PER C.C.	UN-DILUTED	DILUTIONS 1:2	1:4	1:8	UN-DILUTED	DILUTIONS 1:2	1:4	1:8
R. B.	*Streptococcus viridans*	10/24/46	5	10.24	+	+	+	+	2:1			
		11/11/46	5	10.24	±	+	+	+	2:1			
		11/27/46	5	40.96	0	0	+	+	8:1	4:1	2:1	1:1
		1/14/46	5	5.12*	+	+	+	+	1:1			
H. W.	*Streptococcus viridans*	1/14/46	10	12.80	+	+	+	+	1.25:1			
		1/17/46	10	40.96	0	+	+		4:1	2:1	1:1	
		1/19/46	10	25.60	+	+	+		2.5:1	1.25:1	0.6:1	
		1/23/46	10	40.96	0	+	+		4:1	2:1	1:1	

0, No growth; complete inhibition.
±, Good inhibition of growth but incomplete.
+, Growth; no effective inhibition.
*Prophylactic level for oral surgery, subsequent to treatment for subacute bacterial endocarditis.

serum level determinations in duplicate. The method is similar to that described by Rammelkamp* and others, and we employ routinely as our standard a strain of *Staphylococcus aureus*. The first set of tubes is inoculated in the usual manner with a 1:1000 dilution of a six-hour broth culture of this standard organism. The second set is similarly inoculated with a broth culture of the patient's own organism, diluted to give approximately the same number of organisms per cubic centimeter of diluent.

Typical findings in two cases are outlined in Table I. As shown, our results indicate that the serum level necessary to inhibit completely the growth of the patient's own organism in these cases was approximately the equivalent of four times the determined sensitivity of the organism. Serum dilutions having fewer Oxford units per cubic centimeter, even in ranges considerably above the actual sensitivity in vitro, showed graduated increases in the amount of growth (observed in stained smears), though the increase was never comparable to that of the control tube. Concurrent redeterminations of the sensitivity of the specific organism to penicillin in pure broth were occasionally made as a check and also to eliminate possible changes due to subculture on artificial media.

Patients with resistant organisms treated in this manner have achieved and maintained "clinical cures." Both patients on whom data are given in Table I became completely bacteria free under a therapeutic regimen based on the necessary levels of serum penicillin indicated by this test. Patient H. W. died of unrelated causes without a recurrence of the bacteremia. Patient H. B., who had subacute bacterial endocarditis, is of particular interest because he had been treated elsewhere on several occasions with the usual empiric type of therapy; on each occasion there was a relapse, with the reappearance of a *Streptococcus viridans* strain in blood cultures. With intensive therapy, which maintained levels for protracted periods of time sufficiently high to inhibit his own organism, a "clinical cure" was achieved, and he is back at work. He has remained free of any sign of infection for one year. At times, higher levels than necessary were reached, but complete inhibition of his strain of *Streptococcus viridans* was then obtained in all dilutions within the effective range.

As a result of these findings, we suggest that, in the treatment of resistant cases of bacterial endocarditis or acute septicemia with penicillin, therapy should be adequate to maintain, for a considerable period, serum levels sufficiently high to be completely bacteriostatic for the patient's own organism, as determined directly in vitro. This type of planned therapy will insure an optimal therapeutic level being reached in the blood stream.

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COAGULATION OF THE BLOOD IN LUSTEROID TUBES: A STUDY OF NORMAL PERSONS AND PATIENTS WITH ARTERIAL OR VENOUS THROMBOSIS

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THE introduction of anticoagulant therapy has created new interest in thrombosis and the relation of increased coagulability of the blood to the development of this condition. Unfortunately, however, the various tests developed for measuring the clotting time, while valuable in determining a prolongation, do not allow for accurate measurement of acceleration of the process. Indeed, ordinary determinations of coagulation time of whole blood usually give normal results. There would appear, therefore, great need for a test that would detect a shortening of the coagulation process. Because of this, a concerted effort has been made in recent years to develop such a procedure. The result is that several tests have been proposed. Each of these is, in its own way, time consuming and at best measures but one aspect of a complex reaction, often by the addition of heparin, thromboplastin, etc., substances with a not fully understood effect on the clotting process.

As a result it was felt worth while to study coagulation in vitro under conditions simulating as closely as possible coagulation in vivo; in other words, without the addition of substances concerned in coagulation.

To do this the coagulation time of blood in lusteroid (synthetic plastic resin surface) tubes was studied. These tubes were chosen because of the prolongation of coagulation time in them. Thus, with deceleration of the process, accurate measurement of significant decreases in coagulation time might be possible.

In this study, which includes a review of the pertinent literature on the subject, I have attempted (1) to establish normal values for the test, (2) to ascertain the reliability of the test, (3) to use the test in the study of arterial and venous thrombosis, and (4) to use the test in the study of patients receiving anticoagulant therapy. The first three points will be considered in this paper. The last will be taken up in a subsequent paper.

REVIEW OF LITERATURE

Tests Used for Detection of a Tendency to Thrombosis.—Chantemesse[1] in 1909 and Gelera[2] in 1921 devised a test of coagulation time based on the observation

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that specimens of "good clot forming ability" require a higher concentration of anticoagulant solution in order to prevent coagulation as compared with specimens of "poor clot forming ability." In Chantemesse's test, a minute volume of blood was mixed with the same volume of solutions of potassium oxalate in increasing concentrations of from 1:1800 to 1:400. This series of mixtures of blood and oxalate was placed in capillary tubes. In one hour the tubes were inspected and the lowest concentration of oxalate which had prevented coagulation was noted. Since this minimal concentration in a normal case is a 1:800 solution of oxalate, a specimen of blood requiring a stronger solution for prevention of coagulation was considered to have better than normal coagulating ability.

More recently, de Takats and Gilbert[3,4] made use of this principle in studying patients who had had arterial or venous thrombosis. Ten milligrams per cubic centimeter of heparin was injected intravenously and coagulation times were determined in capillary tubes at ten-minute intervals for forty minutes. They found the resistance to heparin marked (1) in the early postoperative period, (2) after cardiovascular accidents, and (3) in thromboangiitis obliterans. The blood of thirty-six patients showed heparin resistance in the immediate postoperative period for an average of four days; that of eighteen patients who had coronary thrombosis, cerebral thrombosis, arterial embolism and venous thrombosis, from whom samples of blood were taken within a few days after the occlusion, showed heparin resistance. In nine patients in whom blood was drawn weeks or months after the accident the response was normal. Six patients who had thromboangiitis obliterans were, without exception, classed as hyporeactors to heparin. De Takats[3,4] further claimed that unless the disease was in the stage of complete remission, patients who had thromboangiitis obliterans might be expected to give such a response. Hyporeactors were defined as those patients whose capillary coagulation time ten minutes after the injection of heparin did not rise to more than 4.5 minutes and hyperreactors as those whose capillary coagulation time rose to more than 7.5 minutes in the same interval of time.

Waugh and Ruddick,[5,6] by an in vitro technique involving use of increasing concentrations of heparin in a series of tubes to which 1 c.c. of blood to be studied was added, were able to construct curves by plotting units of heparin against coagulation time in minutes. These curves clearly illustrated an acceleration of the velocity of coagulation (1) during uncomplicated rest in bed, (2) after operation, (3) in acute inflammatory conditions, such as pneumonia, and (4) after severe hemorrhage. They also were able to demonstrate a slowing of coagulation during radium therapy for carcinoma of the cervix.

Hagedorn[7] has devised an in vitro procedure which is simple, and he is of the opinion that it is reliable. It involves use of 0.5 c.c. of saline solution, 1 c.c. of blood, and 0.005 mg. of heparin. The normal range of coagulation time with his method is forty-five to eighty minutes.

Brambel and Loker,[8-10] recognizing the need for the detection of the tendency to intravascular clotting before the appearance of thrombotic phenomena, proposed a test based on the prothrombin activity of serial dilutions of plasma. Essentially they modified Quick's method of determining prothrombin time by

using 12.5 per cent plasma. They stated that differences in clotting activity of the blood in normal and pathologic states cannot be demonstrated in undiluted plasma because of shortness of the clotting interval and limitations of experimental error. This is in agreement with Link,[11] who pointed out that prothrombin time of 12.5 per cent plasma will indicate the onset of hypoprothrombinemia before whole plasma will. The eightfold dilution prolongs the normal time. Using this method, Brambel found a significant shortening of the prothrombin time in thrombophlebitis, coronary thrombosis, and diabetic and frostbite gangrene. These observations were, in a way, compatible with the results of the heparin tolerance tests and indicated the action of substances other than thromboplastin and probably other than prothrombin alone. The advantages claimed for this test are that it can be carried out by a laboratory technician and that a reading can be ready in seconds instead of many minutes. De Takats,[12] however, has found that in his laboratory the end point of this procedure "is difficult to read and interpretation of the shorter than normal prothrombin times unclear."

Von Kaulla and Olivier[13] and Mülly[14] reported on the use of Lenggenhager's thrombin disintegration reaction in the detection of postoperative thrombosis. This reaction is based on the principle that the addition of defibrinated blood to recalcified citrated blood results in shortening of coagulation time to a value read in seconds. This value is similar to that which occurs on the addition of thromboplastin in the ordinary test of prothrombin time. They postulated that the shortening of the coagulation time in their test is due to the "thrombin" content of the defibrinated blood. They further showed that the use of blood thirty minutes after defibrination in this process resulted in a longer coagulation time than use of blood immediately after defibrination. This increase in coagulation time, they postulated, was due to antithrombin activity. Normal values for coagulation time were established as sixty seconds for thirty minutes after defibrination and 112 seconds for sixty minutes after defibrination. Von Kaulla and Olivier and others considered a postoperative coagulation time of less than forty seconds (thirty minutes after defibrination) as suggestive of a tendency to thrombosis. In thirty-three postoperative cases coagulation times of twenty to thirty seconds were obtained. They considered a coagulation time of less than seventy seconds (one hour after defibrination) as suggestive, and one of less than sixty seconds has been claimed as proof of thrombosis. The postoperative shortening of coagulation time as measured by this method they interpreted as being due to a postoperative decrease in the "antithrombin" content of blood.

Effect of Surface on Coagulation.—A good many investigations have been carried out on the influence of external physical factors on coagulation. The problem of surface effect has been among the most significant of these since Freund,[15] in 1886 demonstrated increased coagulation time for blood collected in vessels lined with petrolatum. Bordet and Gengou[16] were of the opinion that the retardation of coagulation in oiled or paraffined test tubes as compared to that in untreated tubes was due to the fact that paraffin was not "wettable" by blood. Pickering and de Souza[17] stated that clotting was due to lysis of a colloidal complex and that these surfaces (oil or paraffin) impeded such lysis. Gortner and

Briggs,[18] using streaming measurement of electric potential (method involves forcing fluid through the pores of a diaphragm or capillary tube and measuring the potential set up across the diaphragm), showed that a bare glass capillary tube had a negative potential of approximately 30 millivolts. This potential was essentially zero (0) when the capillary tube was coated with paraffin. This substance would favor the absorption of positively charged colloids on the interface of the glass and blood serum. They postulated, then, that the initial step in blood clotting involves a surface concentration of some positively charged constituent and that the concentration is brought about by selective absorption.

Lampert[19,20] and Neubauer and Lampert,[21] using a method by which they could obtain a measurement of the surface tension of the blood in tubes of different materials, found definite relationship between coagulation time and surface tension of the blood in a particular container. As a result of this, Lambert began a search for test tubes of a material in which the relative surface tension of the blood would approach that in a paraffined test tube. This led him to the field of synthetic resins and he found a plastic synthetic surface similar to bakelite, called "athrombit," which he showed was superior to paraffin in its ability to delay coagulation. He constructed hematologic apparatus of athrombit, including a pipette for counting platelets, containers for direct transfusions of blood, special syringes. According to his technique the normal coagulation time for human blood at 37° C. is approximately thirty minutes in athrombit tubes.

Lampert's work also disclosed that various glass surfaces produced different effects on coagulation time; the poor glass which contained relatively much alkali produced a hastening of the process. This work resulted in the so-called Lampert's law; namely, that the anticoagulant power of a surface is inversely proportional to the force of adhesion exerted between that surface and water. The figures of Hirschboeck[22] are of interest in this connection; he found that (1) force of adhesion of "lucite" or methyl methacrylate and water (capillary tube method) equals 0.038 Gm. per centimeter, (2) force of adhesion for paraffin and water equals 0.037 Gm. per centimeter, and (3) force of adhesion for glass and water equals 0.053 Gm. per centimeter. Hirschboeck[23] has shown, however, that, contrary to Lampert's law, coagulation time of normal human blood on a collodion surface is longer than on a paraffin surface even though the force of adhesion between blood and collodion is much greater than that between blood and paraffin.

Lozner and associates,[24] using normal platelet free human plasma (obtained through high speed centrifugation in lusteroid tubes) to which no anticoagulant was added, reported that the effect of glass surface "could not reasonably be attributed to lysis of platelets." Thus, by using 2 ml. of plasma they found the following average figures for coagulation time: (1) in glass, eleven minutes; (2) in collodion, sixty-four minutes; (3) in paraffin, forty-four minutes, and (4) in lusteroid, forty-nine minutes. By placing plasma rich in platelets (obtained by slow centrifugation in 2.5 per cent sodium citrate) in the four different tubes at room temperature for one hour, these workers found no significant change in platelet counts at the end of this period. Nevertheless, the coagulation time of plasma exposed to glass one hour prior to recalcification was markedly less than

that obtaining for the other three samples exposed for the same time to other surfaces. They then took 2 ml. samples of citrated platelet free plasma and found that on recalcification coagulation time in glass was normal, whereas those exposed to the other three surfaces had markedly prolonged coagulation times. Next, using normal citrated plasma rich in platelets prepared without exposure to glass and transferred to the four tubes, they found that the sample exposed to glass had much greater clot promoting power for hemophiliac blood than did the other samples. Then this experiment was repeated with platelet free plasma and the same results were obtained. These investigators were able to note also that plasma placed first in glass vessels before transfer to one of the other surfaces behaved as plasma exposed to glass alone. They speculated that the so-called physiologic anticoagulant sought by many investigators as an explanation for the fluidity of blood may be found in the vascular endothelium which may resemble such surfaces as collodion, paraffin, and lusteroid in its behavior toward some noncellular plasma constituent as Gortner and Briggs, whose work has already been referred to, concluded.

Tocantins,[25] taking note of the longer plasma coagulation time in paraffin, collodion, lusteroid, and acryloid tubes than in glass, followed an interesting line of reasoning. He noted that normal plasma has the property of reducing the clot-accelerating action of the cephalin fraction of thromboplastic lipoprotein derived from homologous brain extracts and classified this as "anticephalin" activity. He showed that dilution of plasma (up to 20 per cent) or exposure to adsorbents decreased this anticephalin activity. He further found that either of these procedures, dilution up to 20 per cent, or absorption of plasma before placing it in the four tubes of varying surface, decreased the difference in coagulation time between that in glass and other vessels. He thus concluded that the extent of the difference in coagulation time between glass and the other surfaces was an approximate measurement of "anticephalin" activity.

Coagulation Time of Blood in Arterial or Venous Disease.—Shafiroff and co-workers,[26] using a modification of the Lee-White procedure for determining coagulation time, studied twenty-eight normal persons and found a slight tendency for blood from a lower extremity to clot faster than blood from an upper extremity. They further found this tendency exaggerated moderately among 156 patients who had varicose veins and exaggerated markedly in the blood of seven patients who had thrombophlebitis. Di Cio and Bay[27] reported a study of coagulation time by the Lee-White method in cases of intermittent claudication and gangrene of the legs. They divided their cases into four groups. In Group 1, which consisted of nineteen patients with intermittent claudication, coagulation time was short in ten patients (53 per cent) and normal in the remaining nine (47 per cent). Group 2 was made up of patients with intermittent claudication and essential hypertension; the coagulation time was short in twenty-two of thirty-two patients studied. Group 3 consisted of eighteen patients with gangrene of a lower extremity. In ten (55 per cent) coagulation time was decreased. Group 4 contained ten patients with gangrene of a lower extremity and arterial hypertension. In six (60 per cent) the coagulation time was shortened.

Theis and Freeland[28] studied the superficial venous and arterial blood in seven patients with acute thromboangiitis obliterans. They found (1) increased viscosity of blood, (2) rapid sedimentation rate, (3) rapid coagulation, (4) increased alkalinity, (5) low or normal cell counts, (6) low oxygen saturation of arterial blood, and (7) a low carbon dioxide content of the blood. They suggested that the anoxia could account for the hypercoagulability "just as rapid clotting in asphyxia is the result of deficient oxygen supply, according to Cannon and Mendenhall."[29]

Davidson and MacDonald[30] found that after administration of dicumarol the coagulation time measured in lusteroid tubes, although more variable than when it was measured in glass, was much greater than that obtained in glass. The suggestion was made that the coagulation time in lusteroid tubes indicates the true coagulation defect more closely than does the coagulation time in glass. They noted no strict parallelism between coagulation time in lusteroid tubes (or glass) and concentration of prothrombin, and, furthermore, some of the patients had a moderately prolonged coagulation time in lusteroid without any profound lowering of prothrombin concentration. Similar studies which I carried out are to be reported in an ensuing paper.

PROCEDURE USED IN THIS STUDY

The following equipment was used: (1) a 5 c.c. syringe well lined with mineral oil and size 20 needle, lined with mineral oil; (2) tourniquet, (3) alcohol and sponge, (4) lusteroid tubes (12.5 mm. in diameter), and (5) Lee-White glass tubes (8 mm. in diameter).

The tourniquet was applied briefly above a large antecubital vein. The needle was inserted quickly into the vein with a minimum of trauma. If the vein was not punctured in the first attempt, the needle was withdrawn and another vein was used. The tourniquet was immediately removed and blood was withdrawn. The time at which the blood was first drawn into the syringe was noted. It was important that no bubbling or frothing occur within the syringe. If this occurred, the specimen of blood was discarded. Three cubic centimeters of blood were obtained; 2 c.c. were transferred to a lusteroid tube and 1 c.c. to a Lee-White glass tube. The tubes were tilted every thirty seconds. Coagulation was assumed to be complete as soon as the tube could be inverted without displacing the clot. It was important that the temperature be relatively constant. Throughout this work the tests were carried out at a room temperature of 24° to 26° C. Occasionally the tube was inverted without displacing the clot and yet the blood was liquid beneath the surface clot, as noted by free movement of a bubble within it. For these specimens the coagulation was considered complete the moment that the clot was firm throughout, as noted by the freezing of the bubble. The normal Lee-White coagulation time, according to this procedure, was considered to be 5 to 10 minutes, although many normal persons have a Lee-White coagulation time in the range of 4 to 12 minutes.

For cleaning tubes a soft brush was used. Tubes were rinsed thoroughly in hot water after cleaning with sodium lauryl sulfonate. They then were rinsed four times in distilled water and dried by inversion over night.

RESULTS OF TESTS

On Normal Persons.—The control group consisted of fifty subjects. Most of these were healthy, active adults, nurses, technicians, and physicians, and eighteen were ambulant patients who had conditions, such as duodenal ulcer, which would not affect the coagulation time of the blood. For purposes of this study these eighteen patients were considered normal and will be referred to in this way. Ages of these persons ranged from 18 to 40 years. There were twenty-seven men and twenty-three women. The results of the study of these normal subjects are shown in Table I. The coagulation time ranged from 14 to 28 minutes. The mean value was 19 minutes. The coagulation time of the blood of twenty-six subjects was 18 minutes or less and of twenty-four was 19 minutes or more.

TABLE I. NORMAL VALUES

COAGULATION TIME IN LUSTEROID TUBES (MIN.)	FREQUENCY
14	1
15	6
16	3
17	7
18	9
19	7
20	3
21	4
22	3
23	4
25	2
28	1
Total	50

Tests of the coagulation time of the blood of five normal persons were made in new lusteroid tubes and these results were compared with those obtained for five normal subjects when the test was made in lusteroid tubes of the original batch which had been washed one or more times. The results are shown in Table II. Although the sample is small, it is apparent that slightly longer

TABLE II. COMPARISON OF RESULTS OBTAINED IN NEW AND OLD LUSTEROID TUBES

NEW TUBES		OLD TUBES	
TUBE	COAGULATION TIME (MIN.)	TUBE	COAGULATION TIME (MIN.)
1	22	1	23
2	18	2	20
3	18	3	19
4	28	4	20
5	25	5	18
Mean	22.2	Mean	20.0

coagulation times and a slightly longer mean occurred when new tubes were used. This increase is, however, within the range of experimental error of the test (Table III).

To ascertain further the reliability of the lusteroid procedure as outlined previously, it was decided to study coagulation time in each of ten tubes, using a part of the same sample of blood in each tube. For this purpose 20 c.c. of blood were drawn from each of two normal young adults and 2 c.c. were placed in each tube. There was a maximal variation of 2.5 minutes (Table III), exclusive of any consideration of variation due to blood first leaving vein as against that most recently leaving the vein in the 20 c.c. samples used.

TABLE III. RELIABILITY OF TEST USING NORMAL SUBJECTS

CASE 1		CASE 2	
LUSTEROID TUBE	COAGULATION TIME (MIN.)	LUSTEROID TUBE	COAGULATION TIME (MIN.)
1	17.5	1	23.0
2	17.5	2	22.0
3	20.0	3	22.0
4	18.0	4	21.5
5	18.0	5	22.0
6	18.0	6	23.0
7	18.0	7	23.0
8	19.0	8	22.5
9	18.5	9	22.5
10	18.0	10	23.0
Maximal variation:	2.5		1.5

Several months after this investigation was begun a new batch of lusteroid tubes arrived. Their appearance was different from the first batch with which all our results were obtained. The second batch of tubes gave consistently lower coagulation times than did the original, with a range of 6 to 13 minutes under the conditions outlined previously. It was decided, therefore, not to use these tubes in this experiment. This suggests that the normal coagulation time in lusteroid tubes must be obtained for the tubes in use, as was done with the tubes in this study, before any investigation is undertaken. This probably accounts for the great variation of the normal values reported in the literature. A similar variation for glass has been reported by Lampert[19] and is referred to elsewhere in this paper.

In Cases of Arterial and Venous Thrombosis.—The coagulation time of the blood of eighteen patients who had arteriosclerosis obliterans was determined in lusteroid tubes. The results are given in Table IV.

The coagulation time in nine patients (50 per cent) was less than normal by lusteroid method and in four by the Lee-White method (22 per cent). In Cases 3, 4, and 5 acute arterial occlusion had occurred two to three weeks previously. In Case 16 the acute occlusion had occurred ten days before the test;

TABLE IV. ARTERIOSCLEROSIS OBLITERANS

CASE	AGE (YR.) AND SEX	COAGULATION TIME	
		LEE-WHITE (MIN.)	LUSTEROID (MIN.)
3	50 M	7.5	13.0
4	65 M	5.0	18.0
5	63 M	5.0	11.0
6*	60 M	4.0	10.0
7	61 M	6.0	14.0
8	66 M	6.0	12.0
9*	65 M	4.0	10.0
10	50 M	7.0	37.0
11	65 M	5.0	14.0
12*	47 M	4.0	13.0
13	64 F	6.0	11.5
14	76 M	10.0	28.0
15	71 M	9.0	19.0
16	67 F	4.5	6.0
17	65 F	9.0	14.0
18	63 M	6.0	11.0
19	67 M	6.0	23.0
20	61 F	7.0	21.0

*Diabetic patient.

this patient was the one in whom occlusion was the most recent. Marked hyperlipemia was peresent in but one patient (Case 10) at the time of this study. The relation of this condition to the coagulation time in the lusteroid tube of 37 minutes is conjectural.

The coagulation time of the blood in lusteroid tubes was determined in ten patients with thromboangiitis obliterans. The results are given in Table V. In only three of the ten (30 per cent) was the coagulation time as determined in lusteroid tubes less than the normal. By the Lee-White method it was within limits of normal in all patients. In the six patients in whom the disease was

TABLE V. THROMBOANGIITIS OBLITERANS

CASE	SMOKED	AGE (YR.)	COAGULATION TIME		CLINICAL ACTIVITY
			LEE-WHITE (MIN.)	LUSTEROID (MIN.)	
21	Yes	40	6.0	5.0	Active; infected ulcer of toe
22	No	59	5.0	15.0	Inactive
23	No	36	6.5	20.0	Inactive
24	No	39	5.0	23.0	Active with recurrent superficial phlebitis
25	No	42	7.0	14.0	Active; no phlebitis
26	No	37	10.0	25.0	Active with mild migratory phlebitis
27	No	45	8.0	19.0	Arrested
28	No	36	5.0	12.0	Arrested
29	No	36	10.0	13.0	Active; no phlebitis
30	No		6.0	15.0	Active with phlebitis

clinically active, the coagulation time measured in the lusteroid tubes was decreased in only two. In one patient (Case 21), two weeks after cessation of smoking, the lusteroid coagulation time was 10.5 minutes and the Lee-White coagulation time remained unchanged.

The coagulation time of the blood in lusteroid tubes was determined in eleven patients with thrombophlebitis. The results are given in Table VI. In eight of nine patients with acute thrombophlebitis, the coagulation time in the lusteroid tubes was less than normal. Normal coagulation times were found in the two patients (Cases 33 and 36) in whom the phlebitis was subsiding. In one patient (Case 38) with arteriosclerosis obliterans in whom phlebitis of the calf developed while the patient was under treatment for the arterial disease, the lusteroid coagulation time changed from 14 to 7 minutes, but the Lee-White coagulation time remained unchanged at 6 minutes.

TABLE VI. THROMBOPHLEBITIS (EXCLUDING THAT ASSOCIATED WITH THROMBOANGIITIS OBLITERANS)

CASE	PHLEBITIS		COAGULATION TIME	
	TYPE	SITE	LEE-WHITE (MIN.)	LUSTEROID (MIN.)
31	Acute	Iliofemoral	5.0	10.5
32	Acute	Iliofemoral	6.0	8.5
33	Subacute, subsiding eight days after onset	Deep calf	8.0	22.0
34	Acute, hours	Great saphenous	6.0	8.0
35	Acute	Deep calf	5.0	5.5
36	Subsiding	Great saphenous	7.0	19.0
37	Acute	Deep calf	8.0	18.0
38	Acute	Deep calf	6.0	7.0
39	Acute	Iliofemoral	4.5	4.0
40	Acute	Deep calf	5.0	5.0
41	Acute	Great saphenous	6.0	9.0

The reliability of the test in a case in which the coagulation time was decreased is shown in Table VII. The same procedure as that used to determine the reliability of the test on normal subjects was employed (Table III). The blood in this study was from a patient who had thrombophlebitis (Case 35, Table VI).

The variation in coagulation time was never greater than thirty seconds; that is, no greater difference than the time it took to invert the tube once.

Influence of Diameter of the Tube.—Inasmuch as the lusteroid tube has a greater internal diameter than the Lee-White tube, it was important to note how much of the prolongation of coagulation time in the former tube was due merely to greater diameter. To study this, a lusteroid tube and a glass tube of approximately the same size (12 mm. in diameter) as the lusteroid tube (12.5 mm. in diameter) were used. Simultaneous coagulation times were determined with a

TABLE VII. THROMBOPHLEBITIS OF DEEP CALF VEINS (CASE 35)

TUBE	COAGULATION TIME, IN LUSTEROID TUBES (MIN.)
1	6.0
2	5.5
3	6.0
4	5.5
5	5.5
6	6.0
7	6.0
8	6.0
9	5.5
10	6.0

part of the same blood sample in each of these tubes. The Lee-White coagulation time is listed merely for sake of completeness. The results are shown in Table VIII.

A study of the coagulation times in the glass and lusteroid tubes shows that the effect of the lusteroid tube is largely a matter of quality of surface, since this is the only significant variable that could influence the coagulation times in the 12 mm. glass tube and the lusteroid tubes.

TABLE VIII. COAGULATION TIMES IN LEE-WHITE GLASS AND LUSTEROID TUBES

TYPE OF CASE	COAGULATION TIME (MIN.)		
	LEE-WHITE TUBE*	GLASS TUBE (LARGE)†	LUSTEROID TUBE‡
Arteriosclerosis obliterans; femoral occlusion three weeks previously	5	7.5	13.0
Arteriosclerosis obliterans; iliac occlusion two weeks previously	5	11.0	18.0
Arteriosclerosis obliterans; two weeks after acute femoral occlusion	5	6.0	11.0
Arteriosclerosis obliterans	6	10.0	14.0
Acute iliofemoral thrombophlebitis	5	5.0	10.5
Recurrent cerebral thrombosis	6	12.0	12.0
"Burned out" thromboangiitis obliterans	5	10.0	15.0
Diabetes; arteriosclerosis obliterans	4	5.0	10.0
Arteriosclerosis obliterans	7	8.0	21.0
Arteriosclerosis obliterans	4	6.0	21.0

*Eight millimeters in diameter containing 1 c.c. of blood.
†Twelve millimeters in diameter containing 2 c.c. of blood.
‡Twelve and one-half millimeters in diameter containing 2 c.c. of blood.

SUMMARY

Coagulation times in the lusteroid tubes used throughout this work were in the range of 14 to 28 minutes in a series of fifty normal controls. There is apparently no significant variation in coagulation time obtained when new or used

tubes from the same batch were used. However, normal values must be determined for each new batch of tubes before they are put into use.

The reliability of the test varies with the range of coagulation time. In the short range the experimental variation is very small; in the normal range it is somewhat greater.

In nine (50 per cent) of the eighteen patients with arteriosclerosis obliterans studied, the coagulation times as measured by the lusteroid method were definitely less than for the normal subjects. No cases of acute occlusion were studied.

Ten patients with clinically active or quiescent thromboangiitis obliterans with and without phlebitis were studied. In only three (30 per cent) was there any significant decrease of lusteroid coagulation time. These were two of the group of five patients with clinically active cases.

The most pronounced shortening to less than normal of lusteroid coagulation time occurred in the patients with acute thrombophlebitis. It was noted in eight of the nine patients studied. Normal coagulation times were found in the two patients with subsiding thrombophlebitis. It is suggested that determination of the coagulation time in lusteroid tubes may be of value in indicating a tendency to thrombosis.

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COAGULATION TIME OF THE BLOOD IN LUSTEROID TUBES: A STUDY OF PATIENTS RECEIVING DICUMAROL

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THE coagulation time in Lee-White and lusteroid tubes was determined daily in six patients who had received dicumarol for at least two weeks. The method used has been described in a previous paper but will be mentioned briefly here.

A tourniquet was applied above the antecubital vein and the needle was inserted into the vein. The tourniquet was removed and 3 c.c. of blood were withdrawn into the oiled syringe without bubbling or frothing. The time when the blood entered the syringe was noted. Two cubic centimeters of blood were transferred to a lusteroid tube and 1 c.c. to a Lee-White glass tube. The tubes were tilted every thirty seconds and coagulation was assumed to be complete as soon as the tube could be inverted without displacing the clot; if the blood were liquid underneath a clot, however, coagulation was assumed to be complete as soon as the bubble was frozen in place. Tests were made at a room temperature of 24° to 26°C.

Prothrombin times were obtained simultaneously by a modification of the Quick method.

Findings typical of the group investigated are presented graphically in Figs. 1 and 2. The data in Fig. 1 were obtained in the case of a man 62 years of age who had arteriosclerosis obliterans and had suffered from acute occlusion of the iliac artery two weeks before admission. The initial coagulation time in a lusteroid tube was 18 minutes. Coagulation times and prothrombin times were determined daily for a period of fifteen days while the patient was receiving dicumarol.

As in all the cases studied, the coagulation time of blood determined in lusteroid tubes was delayed more than that determined in the Lee-White tubes after administration of dicumarol. The tendency for the coagulation time measured in lusteroid tubes to increase the longer the patient had received dicumarol, despite the fact that the concentration of prothrombin was maintained at a relatively constant level as indicated by the prothrombin time test, is evident. This is at least suggestive that dicumarol may affect the clotting mechanism in more ways than one.

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The data in Fig. 2 were obtained in the case of a man 50 years of age who had hypertensive and arteriosclerotic heart disease. While in the hospital under treatment for this condition he suffered from an acute pulmonary embolism. The coagulation time had not been determined in lusteroid tubes prior to the embolism. It was determined ten minutes and several hours after embolism.

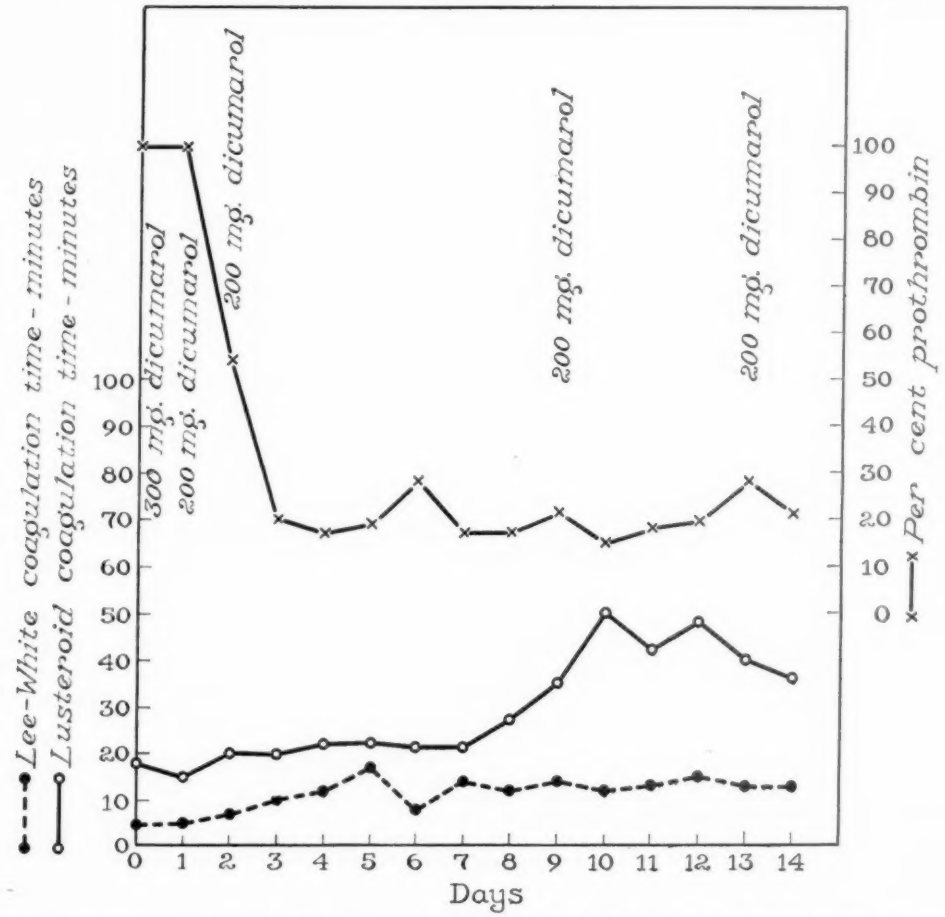
Lee-White coagulation time - minutes
Lusteroid coagulation time - minutes
Per cent prothrombin
300 mg. dicumarol
200 mg. dicumarol
200 mg. dicumarol
200 mg. dicumarol
200 mg. dicumarol
Days
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
0 10 20 30 40 50 60 70 80 90 100

Fig. 1.—Coagulation time and percentage of prothrombin of the blood of a patient who had arteriosclerosis obliterans and was receiving dicumarol because of acute occlusion of the iliac artery.

The patient remained in the hospital an additional two weeks during which period he was given dicumarol. In this case, as in all cases studied, it was evident that there was no strict parallelism between coagulation times determined in lusteroid or Lee-White tubes and the concentration of prothrombin. However, the lusteroid test appears to be more sensitive to changes in coagulation following administration of dicumarol than the Lee-White procedure. An interesting observation is the decrease in lusteroid coagulation time to a value of 14 minutes on the twelfth day (Fig. 2). This was associated with return of pain in the thorax. The pain occurred despite the fact that the concentration of prothrombin on that

day was in the full therapeutic range. The clinical course was suggestive of the possibility of recurrence of embolism.

Coagulation times were determined simultaneously with part of the same sample of blood, using glass and lusteroid tubes of the same size (Table I) in order to test whether the diameter of the tube had any effect on the coagulation time. For these tests 5 c.c. of blood were drawn each time.

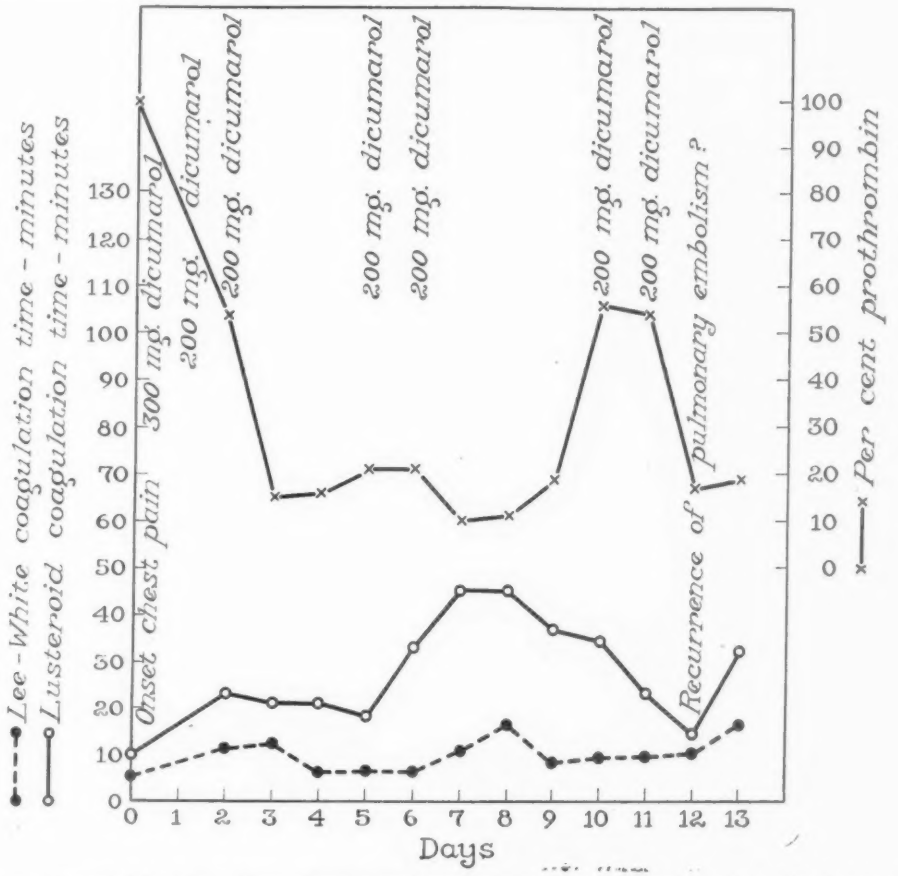

Fig. 2. — Coagulation time and percentage of prothrombin in the blood of a patient who had had an acute pulmonary embolism. Patient was being treated with dicumarol.

The effect of the lusteroid tube was shown to be largely a matter of quality of surface, as this was the only significant variable in the coagulation times determined in large glass and lusteroid tubes in these cases. This corresponds with observations made in a previous paper.

The reliability of the lusteroid test of coagulation time under the condition of prolongation of coagulation time is shown in Table II. For this test 20 c.c. of blood were drawn from a patient who was receiving dicumarol because of acute phlebitis of the leg. Two cubic centimeters of this blood were placed in each of the ten lusteroid tubes. The concentration of prothrombin was 20 per

TABLE I. PATIENTS RECEIVING DICUMAROL

CASE	DOSE OF DICUMAROL, MG.	COAGULATION TIME, MINUTES		
		LEE-WHITE TUBE*	LARGE GLASS TUBE†	LUSTEROID TUBE‡
1	Control§	5.0	11.0	18.0
	300	4.0	10.0	17.0
	200	7.0	8.0	20.0
	200	10.0	14.0	20.0
		12.0	10.0	22.0
		17.0	13.0	21.5
		8.0	11.0	21.0
		14.0	14.0	21.0
		12.0	14.0	27.0
	200	14.0	23.0	35.0
		12.0	17.0	50.0
		13.0	14.0	42.0
2	Control§	5.5	7.5	12.0
	300			
	200	8.0	10.0	16.0
	200	5.5	9.5	17.0
		4.0	12.0	17.0
		6.0	8.0	17.0
		9.0	19.0	21.0
		8.0	15.0	21.0
		11.0	13.0	16.0
		10.0	15.0	21.0
		12.0	18.0	24.5
3	Control§	5.0	6.0	11.0
	300	6.5	8.5	20.0
	200	14.0	12.0	19.0
		18.0	17.0	24.0
		6.0	11.0	17.0
	200	7.0	10.0	20.5
	200	7.0	11.0	19.0
		14.0	16.0	32.0
		12.0	13.0	26.0
		15.0	23.0	35.0

* 8 mm. in diameter containing 1 c.c. of blood.
†12 mm. in diameter containing 2 c.c. of blood.
‡12.5 mm. in diameter containing 2 c.c. of blood.
§Before administration of dicumarol.

TABLE II. RELIABILITY OF TEST IN PATIENT RECEIVING DICUMAROL

TUBE	COAGULATION TIME IN LUSTEROID TUBES, MINUTES
1	28
2	29
3	32
4	33
5	31
6	31
7	31
8	31
9	29
10	30

cent in this sample. Evidence in Table II and in previous work suggests that the test is less reliable, that is, subject to greater variation for patients receiving dicumarol than for normal persons or patients who have a tendency to thrombosis but have not been treated with dicumarol.

COMMENT

These studies of the coagulation time in lusteroid and glass tubes of patients receiving dicumarol largely confirm the previous work of Davidson and MacDonald.* I found that the coagulation time of the blood of these patients was variable and more so when it was determined in lusteroid tubes than in glass. There was no strict parallelism between coagulation time determined in lusteroid or glass tubes and the concentration of prothrombin, and furthermore, some of the patients had prolongation of coagulation time in lusteroid tubes without any pronounced lowering of the concentration of prothrombin. That this might be due to the fact that I did not use diluted plasma in the determination of prothrombin is a matter of conjecture. It has been suggested by others that dicumarol affects fibrinogen, causing a depletion of this substance. So far, however, this work is only suggestive, as no good direct test for determining concentration of fibrinogen has been devised. Throughout the study it was evident that after administration of dicumarol the coagulation time of blood determined in lusteroid tubes showed much greater delay than that determined in glass tubes. There was also a tendency for the coagulation time determined in lusteroid tubes to become longer as the time that the patient received the drug increased despite the fact that the concentration of prothrombin was maintained at a relatively constant level as indicated by the test of prothrombin time.

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*Davidson, C. S., and MacDonald, Harriet: A Critical Study of the Action of 3-3′-Methylenebis (4-Hydroxycoumarin) (Dicoumarin), Am. J. M. Sc. **205**:24, 1943.

AN ELECTROCARDIOGRAPHIC STUDY OF ONE HUNDRED FOURTEEN CONSECUTIVE CASES OF TRICHINOSIS

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THERE have been occasional reports of electrocardiographic changes occurring during the course of trichinosis; for the most part only small numbers of cases have been available for study.[1-4] It has been shown beyond doubt that there is actual invasion of the myocardium by the parasites with a definite, although nonspecific, myocarditis resulting. The pathology has been adequately reviewed by Saphir[5] and by Spink.[2] The electrocardiographic changes are usually transitory, and in the majority of patients the records return to normal. An explanation for this may be found in the study of the pathogenesis of the myocarditis. Dunlap and Weller,[6] working with mice, have shown that although larvae are present in the cardiac muscle early in the disease, no encystment takes place in the myocardium by the time it occurs in the skeletal musculature. They believe that some factor in the heart muscle prevents encystment and that the myocarditis is due to the active migration of the larvae rather than to a blood-borne substance.

Because of the evidence of a definite anatomic process taking place in the myocardium during the disease it may be assumed that the electrocardiographic changes are due to this process rather than to any theoretical toxin or reflex action.

An epidemic of trichinosis broke out on the post at which this general hospital is located and one hundred eighteen patients with this disease were admitted to the hospital. A detailed clinical study of the epidemic is in preparation.[7]

All of the patients were admitted during the acute, invasive phase of the disease. Nearly all showed marked periocular edema and subconjunctival hemorrhages, and complained of muscle pains. There were no fatalities.

Initial electrocardiograms were obtained from 112 patients within three days of admission. All tracings were recorded in the supine position, and the standard limb leads with the addition of CF_2 and CF_4 were taken. Abnormal and borderline records were repeated at approximately weekly intervals until they had returned to normal or until it was not possible to get further records because of the patient's transfer to another installation. Additional electrocardiograms were obtained at random from patients whose initial tracings had

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been normal. This was done in an effort to determine whether or not any changes might occur later in the course of the disease after the actual invasive period was over. Such changes were not found. A total of 255 separate electrocardiograms from the epidemic were available for study. In addition to these records two previous patients are included in the series. These were the only other cases of trichinosis that had been recognized in this hospital.

None of the 114 patients had any signs or symptoms referable to the cardiovascular system. Because of the exigencies of the military situation that prevailed at the time of the outbreak of the epidemic, a complete cardiovascular study could not be made on every patient. However, all patients had a careful physical examination, including blood pressure readings, and were seen daily. All patients whose findings aroused suspicion of clinical cardiovascular disease were referred to the author for further investigation. There were, however, no patients in whom a purely clinical diagnosis of myocarditis was justified.

The criteria for abnormality of the various electrocardiographic complexes were those agreed upon in the standard texts and by the American Heart Association.[8] Several patients who showed RS-T or T-wave variations in Leads I and II when their heart rates were rapid, were restudied on the same day, one hour after administration of 0.2 Gm. of pentobarbital sodium. This was done because it has been observed that in some individuals these changes might be caused by fear or new emotional situations. There were six patients in this group, and all of their records became normal after sedation. Therefore, they are not included in the abnormal group.

FINDINGS

Definitely abnormal electrocardiograms were found in twenty-four of the 114 patients studied (21 per cent). The various abnormalities are listed for each patient in Table I.

P-R Interval.—There were two patients (8.2 per cent) with prolongation of the P-R interval (Table I). In one patient (Case 58, Fig. 1) this was the only definite abnormality, although the QRS voltage was just below the lower limit of normal. The P-R interval was 0.27 second on admission and gradually fell to normal in seven weeks; at the same time the QRS voltage increased. In the other instance (Case 14, Fig. 2), the P-R interval was 0.22 second on admission, increased to 0.24 second on the sixth day, and then returned to normal by the eighteenth day. Associated abnormalities are discussed below and may be ascertained from the illustration.

QRS Duration.—This was prolonged to 0.12 second in seven patients (29.2 per cent), but there were no associated abnormalities in any of the electrocardiograms. All of these patients were followed until their transfer from the hospital three months after admission, and at that time there had been no change in the tracings (Fig. 3).

It might be argued that the QRS duration in these patients was normally 0.12 second, and, consequently, that these records do not represent abnormalities

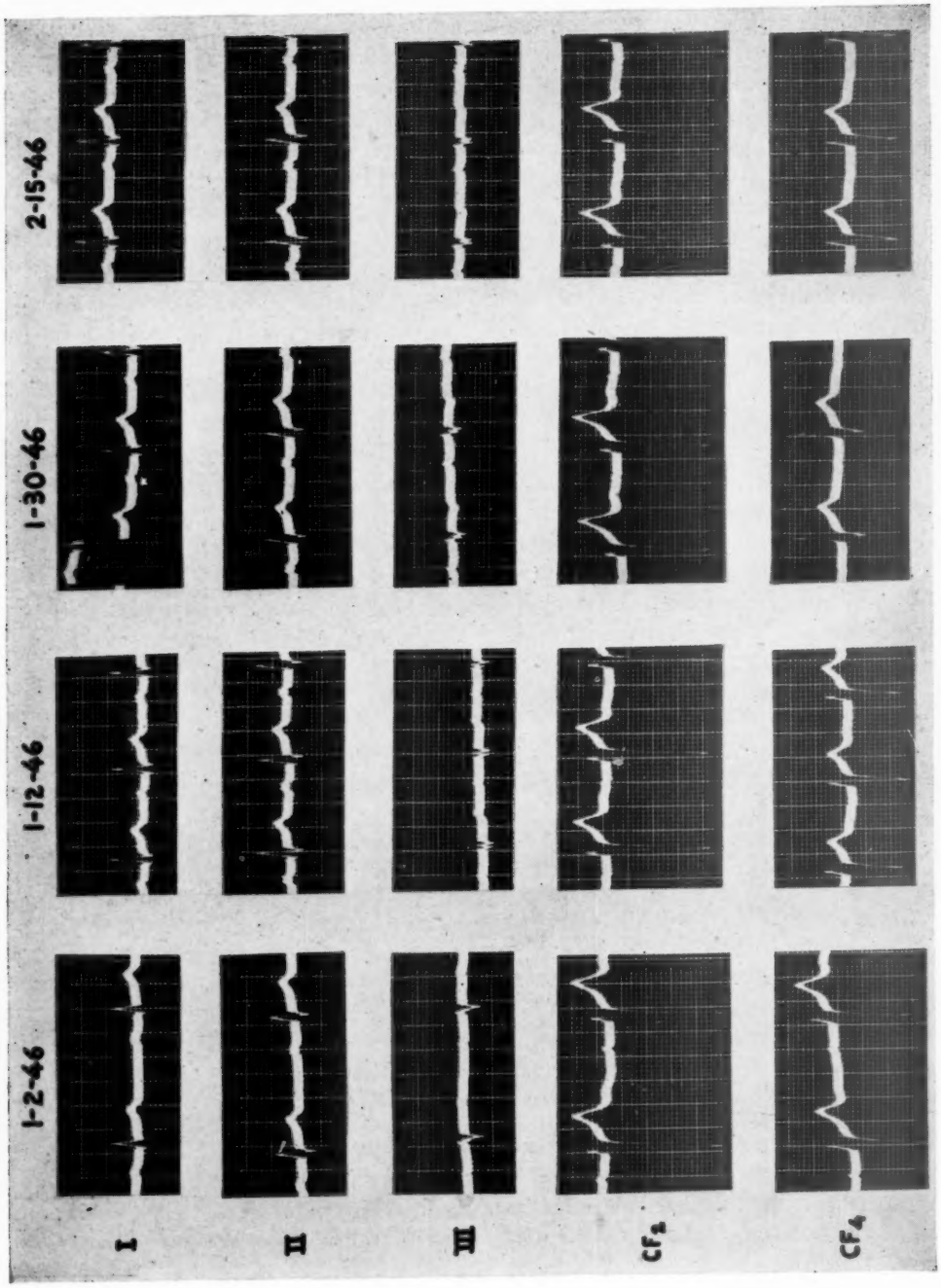

Fig. 1.—Case 58. The P-R interval is prolonged, and the voltage is borderline normal on Jan. 2, 1946. Note the increase in amplitude of the T wave in Lead I although it was never abnormally small. Discussed in text.

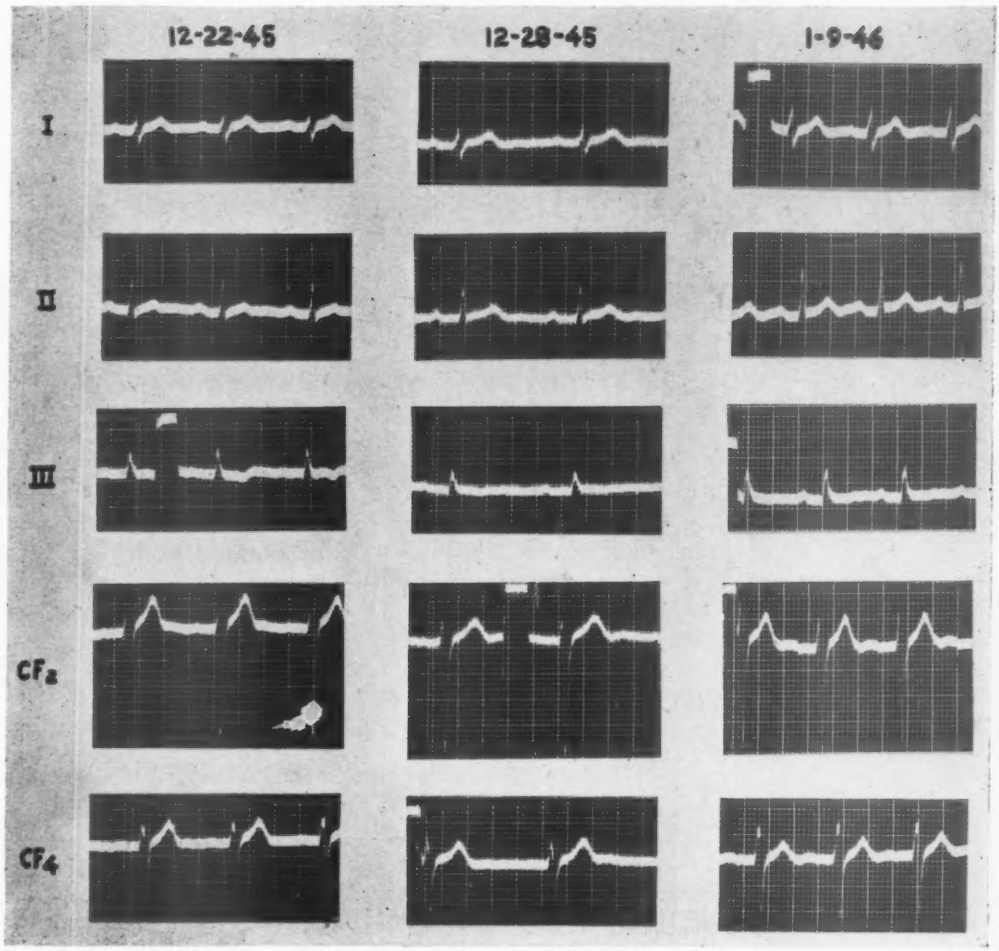

Fig. 2.—Case 14. Prolonged P-R interval increasing in six days and then reverting to normal. There is low voltage of the QRS and a flattened T wave in Lead II. Note the increase in amplitude of the T wave in Lead I. Discussed in text.

which might be attributed to trichinosis. In a survey of 1,000 healthy young aviators in an age group comparable to the present series, Graybiel and co-workers[9] found only eight cases (0.8 per cent) in whom the QRS measured 0.12 second. Ferguson and O'Connell[10] found an incidence of 0.11 per cent among 1,812 young men. Shipley and Halloran[11] found a similar QRS duration in 0.5 per cent of 200 cases, while Hall, Stewart, and Manning[12] found only two instances in which the QRS duration was longer than 0.10 second among 2,000 air force personnel. Graybiel and co-workers[9] conclude that "QRS complexes of 0.12 second duration, even when observed in the electrocardiograms from young, apparently healthy persons, are usually caused by some abnormality, but in rare instances may not have any pathological significance."

TABLE I. ABNORMALITIES WHICH OCCURRED IN EACH OF ABNORMAL ELECTROCARDIOGRAMS IN THE SERIES; CASE 14 HAD AN INITIAL P-R OF 0.22 SECOND ON ADMISSION, AND THIS INCREASED TO 0.24 SECOND ON THE SIXTH DAY

CASE	P-R INTERVAL	QRS VOLTAGE	QRS DURATION	RS-T SEGMENT AND T WAVE	RECOVERY	REMARKS
1	Normal	Normal	Normal	T flattened in Lead II	1 week	T normal in Lead I but amplitude increased
2	Normal	Normal	Normal	Slight S-T depression in Leads II and III. T diphasic in Lead II	1 week	T normal in Lead I but amplitude increased
14	0.22-0.24 sec.	Low in limb leads	Normal	T flattened in Lead II	18 days	T normal in Lead I but amplitude increased
15	Normal	Low in limb leads	Normal	T waves flattened in Leads I and II	2½ weeks	None
17	Normal	Normal	0.12 sec.	Normal	None	No change in 3 months
22	Normal	Low in limb leads	Normal	T flattened in Lead II	2½ weeks	None
23	Normal	Normal	Normal	T flattened in Lead II	1 week	T normal in Lead I but amplitude increased
31	Normal	Normal	Normal	T flattened in Lead II	3 weeks	None
35	Normal	Normal	Normal	T flattened in Lead II	1 week	None
36	Normal	Normal	0.12 sec.	Normal	None	No change in 3 months
40	Normal	Normal	0.12 sec.	Normal	None	No change in 3 months

41	Normal	Normal	0.12 sec.	Normal	None	No change in 3 months
47	Normal	Normal	0.12 sec.	Normal	None	No change in 3 months
50	Normal	Normal	0.12 sec.	Normal	None	No change in 3 months
52	Normal	Normal	Normal	T wave flattened in Leads I and II	1 week	None
58	0.27 sec.	Borderline in limb leads	Normal	Normal	7 weeks	QRS voltage and amplitude of T in Lead I increased
84	Normal	Normal	Normal	T wave flattened in Leads I and II	1 week	None
91	Normal	Normal	Normal	T wave flattened in Leads I and II	1 week	None
95	Normal	Low in limb and chest leads	Normal	T wave flattened in Leads I and II	7 weeks	None
101	Normal	Normal	0.12 sec.	Normal	None	No change in 3 months
102	Normal	Normal	Normal	T flattened in Lead II	10 days	T normal in Lead I but amplitude increased
107	Normal	Normal	Normal	S-T depressed in Leads I and II; T wave inverted in Leads I and II	6 weeks	None
119	Normal	Low in limb leads	Normal	T wave inverted in Leads II and CF_2	3½ weeks	None
120	Normal	Low in limb leads	Normal	Inverted in Leads I, CF_1 (normal), CF_2, CF_3, CF_4, and CF_5; flattened in Lead II	8 days (to borderline normal)	Patient left hospital before recovery

The seven patients in the present series represent 6.1 per cent of the total number of patients studied. This is a far greater percentage than can be found in any of the normal series mentioned and must therefore be considered significant.

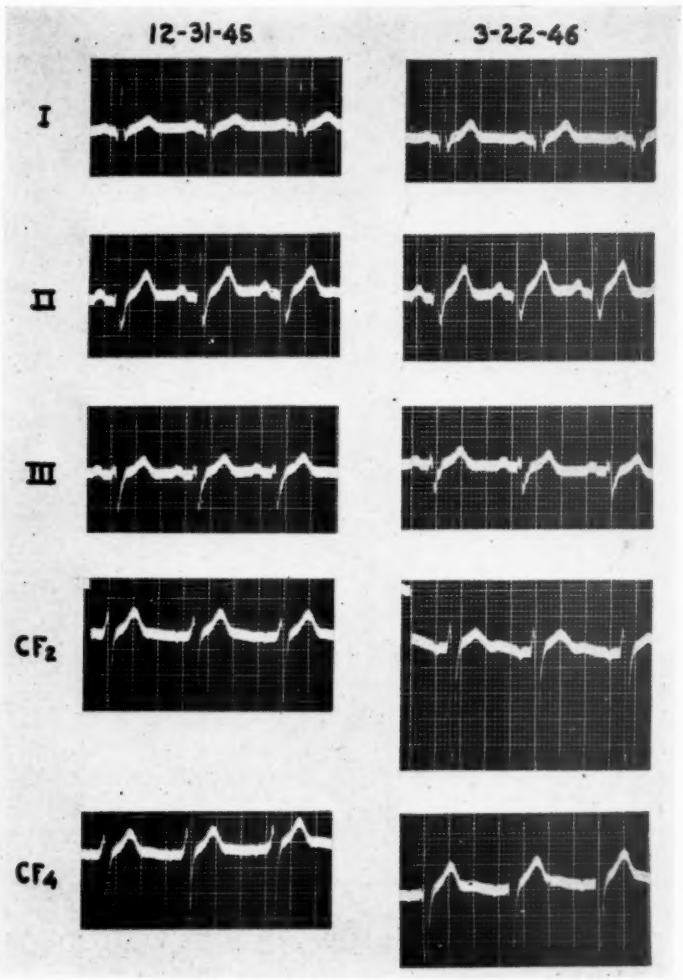

Fig. 3.—Case 17. Persistent prolongation of the QRS duration, 0.12 second. Discussed in text.

QRS Voltage.—Definite low voltage was found in six patients; in five, only the limb leads were involved (Figs. 2 and 4), while in one the chest leads also showed this change (Case 95, Table I). In one additional instance the voltage was borderline if not actually low (Fig. 1), but did show a definite increase as the record returned to normal. In no instance did the low voltage occur as the only abnormality; there were always T-wave changes as well, except in the borderline

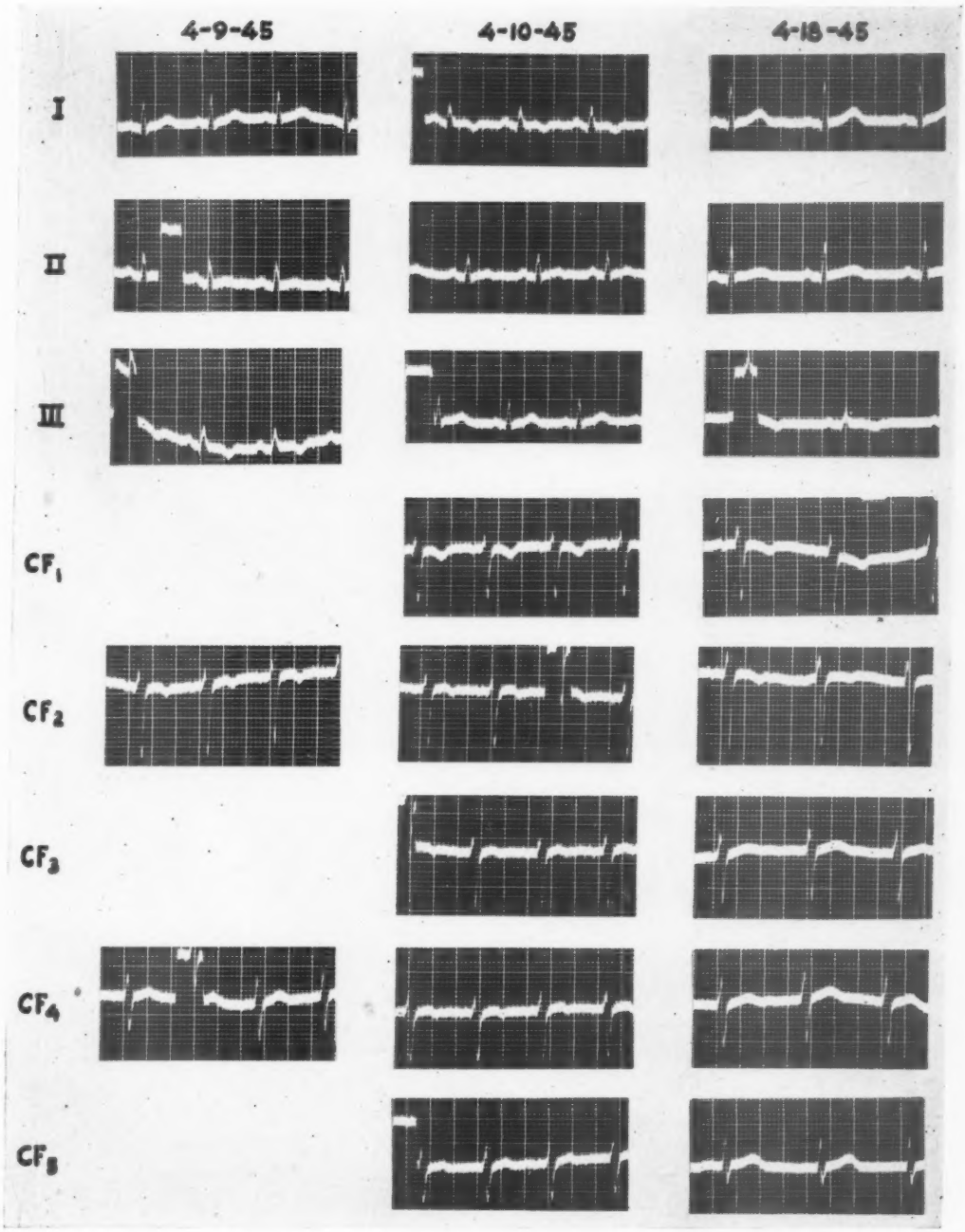

Fig. 4.—Case 120. T-wave inversion in the limb and chest leads. Low voltage of the QRS complexes. The last record still shows residual abnormalities. Discussed in text.

case which showed only a prolonged P-R interval. All of the QRS complexes showed normal voltage as the patients recovered.

RS-T Segment and T Waves.—Inverted T waves in Lead III were not considered to be abnormal since this is a well-known normal variant.

Definite T-wave changes were found in the electrocardiograms of sixteen patients (66.6 per cent). The usual change consisted of a very small, upright T wave (flattened T wave) in Lead II (Figs. 2 and 4). This occurred in thirteen patients and in eight of these was the only T-wave abnormality in the tracings, although other changes were sometimes associated (Table I). In four patients a similar T wave was present in Lead I as well as in Lead II. In one patient T-wave inversion was found in Leads I, CF_1 (normal), CF_2, CF_3, CF_4, and CF_5, while in Lead II the T wave was flattened (Fig. 4).

Inverted T waves were found in three patients (Figs. 4 and 5). In one of these there was definite S-T depression in Leads I and II with inverted T waves in the same leads. In another the inversion occurred in Leads II and CF_2. Case 120 (Fig. 4) has been discussed above. It will be noted that the only indication of T-wave abnormality in the limb leads at the time of the initial electrocardiogram was the flattened T wave in Lead II. Twenty-four hours later T-wave inversion appeared in Lead I.

It is interesting to note that in six cases the T wave in Lead I was always within normal limits, yet showed definite increased amplitude when the tracing had returned to normal (Figs. 1 and 2).

All of the changes in the RS-T segment and T waves reverted to normal in a period ranging from one to seven weeks. There was a rough correlation between the degree of abnormality and the return to normal, inverted T waves taking longer to return than flattened ones.

COMMENT

The only series of cases with electrocardiograms comparable in size to the present one is that of Reimann[1] who studied infected soldiers in a German military hospital. He reported that 75 per cent of seventy-two patients had abnormal tracings during the fifth week after the infecting meal and that the most common finding (in 58 per cent of the cases) was a flattening of the T wave without any other abnormality.

In the present series only 21 per cent of 114 patients had abnormal tracings and the abnormalities were present in the first week of the acute clinical phase of the disease. Our findings of T-wave changes in sixteen patients (66.6 per cent) are roughly in agreement with Reimann's, although in our series this was the sole abnormality in only eight cases (33.3 per cent).

Spink[2] reported that six of eighteen patients (33.3 per cent) had abnormalities which consisted of initial flattening or inversion of the T wave, especially in Lead II, low amplitude of the QRS complexes, and intraventricular block. Contrary to Reimann, he found the earliest changes to occur during the second week of the disease. In our series the findings are in accord with those of Spink.

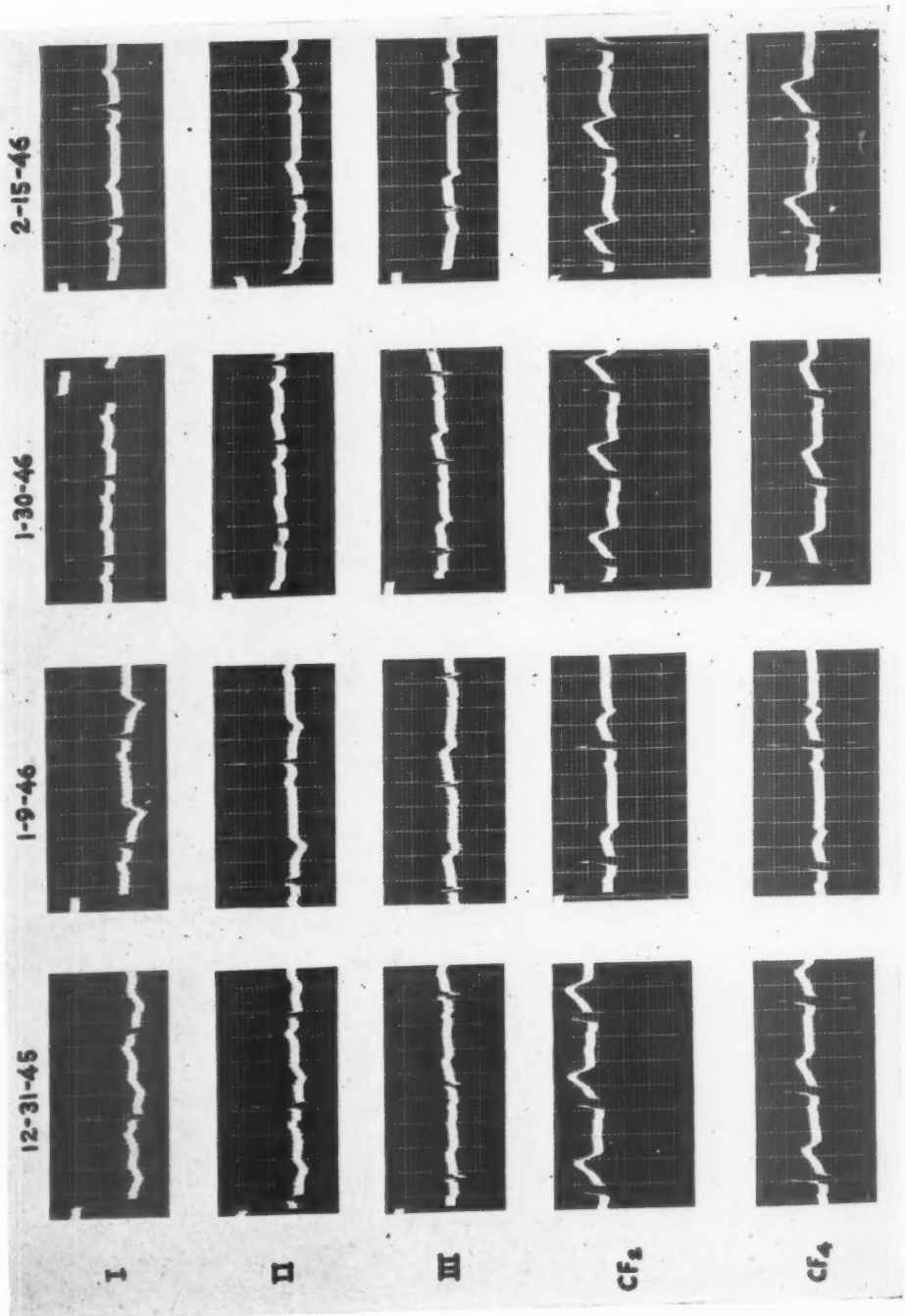

Fig 5.—Case 107. Pronounced RS-T segment and T-wave changes in Leads I and II. Discussed in text.

Among forty-four patients studied by Beecher and Amidon[4] two showed electrocardiographic changes. One had coupled beats due to occasional nodal premature systoles (the significance of which is debatable), and the other showed a prolonged P-R interval.

Master and Jaffe[3] studied four patients and found a P-R interval over 0.20 second in 25 per cent of the tracings and T-wave inversion in 33 per cent. Cushing[13] reported one case showing T-wave inversion, and Polley and Murphy[14] found low voltage of the QRS complexes with T-wave inversion in their single case. In this patient there was persistent T-wave inversion after eight months.

SUMMARY

1. One hundred fourteen consecutive cases of trichinosis were studied electrocardiographically. Definitely abnormal curves were found in twenty-four patients (21 per cent).

2. The main abnormalities consisted of changes in the RS-T segment and the T waves in sixteen patients, (66.6 per cent); prolonged QRS duration in seven patients, (29.2 per cent); low voltage of the QRS complexes in seven patients (including the one borderline case which afterward showed an increase); and prolonged P-R interval in two patients, (8.2 per cent).

3. The only abnormality which consistently occurred alone was the prolonged QRS duration, and this was the only one which did not return to normal.

4. The most common single abnormality was a flattened T wave in Lead II alone or in Leads I and II; this was found in eight patients, (33.3 per cent).

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DISEASES ASSOCIATED WITH LOW CAPILLARY RESISTANCE

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BLEEDING is a symptom which arrests attention. Nosebleeds in rheumatic or hypertensive patients, menorrhagia in purpura, and severe bleeding which follows an operation or minor injury can cause deep concern to both patient and physician. Individuals who show a bleeding tendency usually have a low capillary resistance. The lower the capillary resistance, the greater is the bleeding time.[1] Although some causes of capillary fragility are known, our knowledge on the subject is far from complete.

An analysis is presented of diseases or symptoms found to be present in sixty patients on the day their capillary resistance was extremely low (5 cm. of mercury suction). Solely because of their marked capillary fragility, these sixty patients were chosen for review from among 580 patients in a general practice upon whom some 3,000 capillary resistance determinations were routinely performed. Analysis of these symptoms is given for what light it may shed on factors responsible for undue bleeding.

Capillary resistance was determined with a suction cup apparatus previously described.[2] The minimal amount of negative pressure (suction), applied for one minute to the antecubital space, which produces one petechia or more, is the capillary resistance of the individual. Intervals of 5 cm. of mercury are used, readings being taken from a vacuum gauge. Normal values for capillary resistance are 20 cm., or higher. Definite fragility of capillaries exists when petechiae are produced at 10 cm. of suction, and fragility is extreme when petechiae are produced at a suction of 5 cm. of mercury.

Low capillary resistance has been recorded in scarlet fever,[2,3] measles,[4] scurvy,[5-8] rheumatic fever,[9,10] thrombocytopenic purpura,[1,11] allergic purpura,[12] allergy,[13] asthma,[14] bronchopneumonia,[15] ulcer[16] and colitis,[16] hypertension,[17,18] myxedema,[19] diabetes,[18] during menses or in the premenstrual phase,[20,21,23] and with increasing age.[2,18,22-24]

Extremely low values, 5 cm., have been noted in toxic scarlet fever, early measles, and in the acute stages of purpura and rheumatic fever.

Summaries are presented on sixty patients, all showing extreme capillary fragility (5 cm.) on at least one occasion (Table I). The word "negative" in the column Symptoms on Day of Low Capillary Resistance is used to signify that no symptoms or signs were noted on that particular day to account for the low capillary resistance obtained. Dates are included mainly to allow the reader a chance to interpret a possible sequential relation of disease to capillary resistance.

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TABLE I. CLINICAL FINDINGS IN SIXTY PATIENTS WHO SHOWED DECREASED CAPILLARY RESISTANCE ON AT LEAST ONE OCCASION

CASE	SEX	AGE	PAST HISTORY	DATE OF LOW CAPILLARY RESISTANCE (5 CM.)	SYMPTOMS ON DAY OF LOW CAPILLARY RESISTANCE	NUMBER OF OTHER CAPILLARY RESISTANCE READINGS	RANGE OF OTHER CAPILLARY RESISTANCE READINGS (CM.)
1	M	29	Rheumatic fever, age 16	2/19	Subacute rheumatic fever; urticaria	—	—
2	F	33	Recurrent tonsillitis; sinusitis	9/1	Evanescent pain in legs	—	—
3	M	35	Rheumatic myocarditis; recurrent tonsillitis and sinusitis; bronchopneumonia 3/1	3/24	Negative; ambulant, recovered from bronchopneumonia	2	10-20
4	F	32	Metrorrhagia	1/23	Gastroenteritis; sinusitis; several petechiae on skin	3	10-15; average 10
5	F	38	Severe rheumatic fever and myocarditis, age 19; menorrhagia; bruises easily	3/16	Aching generally; many petechiae (more than 60)	18	10-30; average 15
6	F	17	Chorea; mitral insufficiency	9/15	Rheumatic pains	6	10-20; average 15
7	M	40	Hay fever; rheumatic pains	2/2	Subacute rheumatic fever	2	15-20
8	F	47	Neurasthenia	10/31	Rheumatoid arthritis; fatigue	1	30
9	F	62	Hypertension	1/2	Hypertension (204/162); joint pains; bruises	—	—
10	F	59	Rheumatic pains; prolonged bleeding; hemorrhagic retinitis 1/24; angioneurotic edema	2/7	Rheumatic pains; acute sinusitis; several petechiae	—	—
11	F	43	Rheumatic mitral insufficiency and stenosis	3/3	Aching; many petechiae	—	—
12	F	30	Rheumatic pains	4/14	Rheumatic pains	—	—
				5/29	Negative		
13	F	27	Negative	7/16	Nosebleed; sinusitis; joint pain	—	—
14	F	60	Hay fever; rheumatoid arthritis; recent bruising	8/10	Joint pains; hypertension (180/110); several petechiae	—	—
				8/13	Sinusitis; joint pains; percussion of sinuses produces hematoma		
15	F	34	Easy bruising; obesity	8/13	Rheumatism; fatigue; headache; sinusitis	—	—
16	F	36	Bruises and bleeds easily; rheumatic pains	12/5	Rheumatic pains; neurasthenia	—	—

17	F	60	Bleeds and bruises easily	2/5	Generalized aches; about 30 petechiae	8	10-25; average 15
18	M	42	Rheumatic fever, age 17; syncope 3/7; hypotension (98/70); rheumatic pains	4/5	Negative; no rheumatic pains in past week	—	—
19	F	34	Chronic pansinusitis; colitis; despondent and suicidal; muscular pains	12/6	Depressed; progressive deafness; aprosexia	1	15
20	M	20	Negative; intestinal influenza 2/22	2/27	Acute pharyngitis and bronchitis; hundreds of petechiae this A.M.; positive "flicking" test	1	15
21	F	30	Vertigo; deafness; A.M. headaches; chronic sinusitis; prolonged bleeding	9/27	Acute sinusitis; appears toxic; several petechiae	—	—
22	F	74	Diabetes; chronic sinusitis; recurrent bronchitis; recurrent lumbar myositis	3/12 4/22 5/8	Negative Negative Acute pharyngitis; cervical adenitis	3	10-25; average 15
23	M	40	Chronic sinusitis	6/20	Acute sinusitis	1	10
24	F	22	Chronic sinusitis; subchoreic twitching	9/27	Acute sinusitis; fatigue	6	10-15; average 15
25	F	28	Beginning acromegaly (case reported[25]); numerous lentigines signifying hypoadrenia[26]	3/25	Acute sinusitis; 5 petechiae on skin	1	10
26	F	19	Chronic sinusitis; rheumatic mitral insufficiency	7/6	Acute sinusitis	—	—
27	F	62	Chronic fatigue; vertigo; allergy to foods; precordial and joint pain	1/11	Active sinusitis; extrasystole; telangiectases face; bruises	—	—
28	M	52	Angina pectoris	4/2	Angina pectoris; acute diarrhea; acute sinusitis	—	—
29	F	64	Not obtained	7/28	Fibrinous pleurisy; afebrile; many petechiae	—	—
30	F	40	Chronic sinusitis; vertigo; bleeds and bruises easily; menses every 2 weeks prior to hysterectomy	6/14	Chills; fever 102°; teeth (?); cevitamic acid injected intravenously—15 minutes later capillary resistance still 5 cm.; next day capillary resistance 15 cm.	—	—
31	F	29	Bruises easily; chronic sinusitis; numerous lentigines	7/1	Negative; early pregnancy	—	—
32	F	64	Chronic sinusitis; progressive blindness; retinal hemorrhage 4/1	4/22 5/26	Hypertension (180/120) Hypertension (210/140)	—	—

TABLE I—(CONT'D)

CASE	SEX	AGE	PAST HISTORY	DATE OF LOW CAPILLARY RESISTANCE (5 CM.)	SYMPTOMS ON DAY OF LOW CAPILLARY RESISTANCE	NUMBER OF OTHER CAPILLARY RESISTANCE READINGS	RANGE OF OTHER CAPILLARY RESISTANCE READINGS (CM.)
33	F	47	Negative	2/14	Hypertension (190/110)	—	——
34	F	46	Menorrhagia; hypertension; recent menopausal symptoms	1/16	Hypertension (220/116); no menses 3 months	2	10-15
35	F	67	Rheumatism; hypertension; cerebral hemorrhage, age 65; following limited diet, developed scurvy; spontaneous bruises of hands	11/17	Scurvy; fragility continues despite ingestion of 4 oranges daily in past 3 weeks; hypertension (260/160)	—	——
36	F	46	Eczema neck and ear; vertigo and hives following ingestion of many foods; chronic sinusitis; easy bruising	2/28 5/20	Vertigo; deafness; tinnitus; many petechiae Vertigo; tinnitus; marked fatigue; hypotension (100/64)	7	10-15; average 10
37	F	31	Chronic fatigue; mental depression; chronic sinusitis	9/14 1/17 1/25	Fatigue Depressed Fatigue	8	10-20; average 10
38	M	46	Late latent syphilis	3/10	Fatigue	14	15-40; average 25
39	F	31	Eczema lids; hypertrichosis; numerous lentigines and moles; bruises easily	5/5 5/3 5/11	Fatigue; depressed Negative; several petechiae Negative; several petechiae	—	——
40	F	22	Tachycardia; precordial stabs; vertigo; chronic fatigue; menorrhagia	4/17	Fatigue; mild migraine today; few petechiae	—	——
41	M	38	Recurring peptic ulcer	7/21	Peptic ulcer; 10 petechiae on skin	—	——
42	M	39	Fatigue; sinusitis; easy bruising and bleeding	6/11	Vertigo; tinnitus	—	——
43	F	31	Rheumatic fever, age 11; mitral insufficiency; generalized pains; hay fever	2/6	Vertigo; edema hands; urine, blood pressure, negative; 7 months pregnant	4	15-20; average 15
44	M	35	Various allergies; numerous lentigines	4/5	Hives; several petechiae; epinephrine 1:1000, m. 5, injected subcutaneously; 15 minutes later, capillary resistance 15 cm.	—	——

45	F	28	Migraine; rheumatic pains	3/25	Migraine; 15 minutes after ampule gynergen, capillary resistance 10 cm.	—	——
46	F	46	Acne rosacea; metrorrhagia	3/18	Premenstrual; several petechiae and telangiectases	20	10-25; average 15
47	F	31	Frequent colds	2/28	First day of menses; 5 petechiae	—	——
48	F	30	Negative	6/3	Premenstrual	—	——
49	M	42	Undiagnosed hematemesis requiring 13 blood transfusions in two weeks, at age 40	3/29	Acute rhinitis	7	10-30; average 15
				4/3	Negative		
				4/10	Negative; 4/16 capillary resistance 10 cm.		
				4/25	Negative; splenectomy 6/14, diagnosis Banti's syndrome; capillary resistance 6 days later (6/20) 30 cm.		
50	F	47	Chronic sinusitis; progressive deafness	2/28	Tinnitus; 4 petechiae	—	——
51	F	32	Menorrhagia; metrorrhagia	10/31	Negative; few petechiae	11	10-20; average 15
52	F	42	Thyroidectomy age 38; hyperthyroidism continues	3/23	Hyperthyroidism; asthmatic bronchitis; many petechiae	—	——
53	F	32	Bilateral oophorectomy, age 28; joint pain; bleeds readily; sinusitis; purpuric reaction at site of injection (cold vaccine)	11/26	Negative; blood pressure 106/70	—	——
				1/10	Negative; few petechiae on skin		
54	M	45	Bled 24 hours after extraction of tooth; bruises	2/6	Negative	2	10-10
55	F	26	Bleeds and bruises readily; menses 6 days duration	5/18	Negative; 5 petechiae	1	20
56	F	29	Rheumatic mitral insufficiency; numerous lentigines; anemia	5/29	Early tubal pregnancy with rupture and staining since 4/18	—	——
57	F	45	Recent amenorrhea	10/29	Negative	—	——
				11/6	Negative; not pregnant		
58	F	28	Negative	11/8	Negative; ulcer cervix; moderate leukorrhea	—	——
59	F	50	Cancer rectum; metastasis to liver	10/12	Negative except as noted in history	4	10-20; average 15
60	M	49	Rheumatoid arthritis; asthma	4/3	Negative; more than 40 petechiae	—	——

OBSERVATIONS

Sixty patients exhibited several symptoms or diseases which may or may not have been related to their extreme capillary fragility. These will be briefly discussed.

Rheumatic Pain.—Seventeen complained of joint or muscle pain, usually vague and fleeting, on the day low readings (5 cm.) were obtained. Eleven additional patients gave a history of rheumatic fever or recurring generalized pains. Thus a total of twenty-eight of the sixty patients had, on the day of the low reading or previously, rheumatic or generalized pains. Other patients with rheumatic pain, not included in this report, had either normal or moderately lowered (10 cm.) capillary resistance. In a previous study dealing with ambulant rheumatic children,[9] values of 5 cm. were not uncommon, and abnormal resistances (5 and 10 cm.) were found in 40 per cent of all capillary resistance determinations in February, in contrast to only 5 per cent abnormal resistances in September.

Acute Upper Respiratory Infection.—Nine patients had symptoms suggesting these conditions at the time of the low readings. In five others (included in the rheumatic group discussed in the preceding paragraph) there were also joint and muscle pains.

Hypertension.—Systolic blood pressures of more than 170 mm. mercury were found in four; in two others (included in rheumatic group) there were also joint or muscle pains.

Fatigue.—This was complained of by eight patients. Associated complaints in four of these patients were noted, once each, as follows: rheumatic pains, rheumatoid arthritis, acute sinusitis, and migraine.

Vertigo and/or Tinnitus.—These symptoms were complained of by four patients; several others gave a history of these complaints.

Migraine.—Marked capillary fragility during migraine attacks occurred in two patients (Cases 40 and 45), in one of whom there was associated fatigue.

Allergy.—Hives existed in two patients when low readings were found; one had associated joint pains. In the other (Case 44) capillary resistance rose from 5 to 15 cm. fifteen minutes after injection of five minims of adrenalin.

Menses.—One woman was in the first day of her menstrual flow; two other women were in the premenstrual phase (within two days of the expected menses). Many others were tested both during menses and in the premenstrual phase. Normal values were usually encountered; not uncommonly low capillary resistances (10 cm.) existed, but these cases are omitted since minimal values (5 cm.) were not reached.

Bruising and Bleeding.—Ecchymoses as a result of insignificant trauma were noted on the skin of five patients at the time their low capillary resistance was

found. One of the patients had scurvy and another had a proved Banti's syndrome. A history of easy bruising or bleeding was obtained in twenty-one others. Such history included menorrhagia, metrorrhagia, prolonged bleeding following tooth extraction or shaving, spontaneous nosebleeds, and retinal hemorrhage (Case 32).

Petechiae.—More than three petechiae were present on various parts of the skin in twenty-two of sixty patients; of these patients seven showed four to nine petechiae, eight showed ten to thirty petechiae and seven had more than thirty petechiae. Subacute bacterial endocarditis was not present in any of these patients.

Telangiectases.—Two patients had telangiectases of the face.

Miscellaneous Conditions.—A single instance of marked capillary fragility was found in a young man whose chief complaint was an acute petechial rash of the face associated with acute pharyngitis (Case 20). In another patient marked fragility existed with afebrile pleurisy (Case 29).

Seasonal Variations.—Marked capillary fragility occurred more often in the winter and spring, forty of sixty low readings occurring in the first six months of the year. A corresponding seasonal variation in capillary resistance has been previously reported.[9,27]

CONCLUSIONS

1. One may observe marked capillary fragility quite commonly. It existed on at least one occasion in sixty of 580 unselected patients on whom some 3,000 capillary resistance determinations were made.
2. Infection, either low-grade or acute, was often present at the time when low capillary resistance was noted. The most common accompanying condition was vague, indefinite joint and muscle pains. Less commonly acute upper respiratory infections were present.
3. Twenty-three of the sixty patients gave a history of easy bleeding or bruising, or both.
4. Associated conditions noted in patients with extreme capillary fragility were, in approximate order of frequency, fatigue, hypertension, vertigo, allergy, and menstruation.
5. For unknown reasons the degree of capillary fragility is variable in the same person from time to time.
6. There is as yet no satisfactory explanation for the marked capillary fragility existing in many patients.

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THE ELECTROCARDIOGRAM IN MAN DURING AN EPISODE OF CHILL AND FEVER INDUCED BY INTRAVENOUS TYPHOID VACCINE

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THE recent medical literature shows evidence of a growing interest in the cardiovascular changes which occur during the course of infections. Published studies of the electrocardiographic alterations during infections are numerous.[1-8] The changes consist of shortening or prolongation of the P-R interval, decrease in voltage of the QRS complex, a relative increase in the Q-T interval, and alterations in the T wave and S-T segment. The interpretations of the latter changes have neglected the effects of fever, heart rate and position, alterations in acid-base balance, and many other influences. In published clinical studies, furthermore, it is often impossible to distinguish the effects of fever, per se, from those of myocardial changes due to infection itself, anoxia, salt and water depletion, malnutrition, and other unknown factors.

Reports[9,10] based on studies made during physically induced fevers do not yield comparable data, for fevers so induced do not pass through the four phases of the febrile reaction to infection.[11] Physically induced fever lacks the initial prodrome and chill phases characteristic of the febrile reaction to disease;[12] in the chill phase, pronounced vasoconstriction in the skin, kidney, and brain, decreased cardiac output, and increased arteriovenous oxygen difference occur.

It is, therefore, considered of interest to report a study of electrocardiograms obtained during the course of fever induced by typhoid vaccine in human subjects.

MATERIAL AND METHODS

Nine subjects, six of them men, varying in age from 25 to 63 years, were given typhoid vaccine intravenously for therapeutic purposes. The diagnoses were rheumatoid arthritis (Cases 1, 2, 4, 8, 9); tabes dorsalis and general paresis (Cases 5, 7), lymphedema of the face of unknown etiology (Case 6), and subacute bacterial endocarditis (Case 3). In six patients (Cases 1, 4, 5, 6, 8, 9) no evidences of cardiac or pulmonary disease were present. In Case 2, a primary adenocarcinoma of the right lower bronchus with atelectasis and bronchiectasis was

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present; no evidence of heart disease was found. In Case 7, x-ray examination showed moderate cardiac enlargement and aortic dilatation and tortuosity. In Case 3, subacute bacterial endocarditis, rheumatic heart disease, mitral stenosis and insufficiency, aortic insufficiency, cardiac enlargement, and normochromic anemia were present. The studies were made under basal conditions. The patients were recumbent at an angle of approximately 15° with the electrodes in place throughout the experiment; the routine limb and IV F leads were recorded before the injection of the vaccine, and at varying periods thereafter.

Electrocardiograms were taken in each of the four phases of the febrile reaction: (1) prodrome, (2) chill, (3) flush, and (4) defervescence. In two instances 100 per cent oxygen was administered by means of a Boothby mask, at a rate of 10 liters per minute, beginning ten minutes before the injection of vaccine and continuing throughout the febrile course.

The electrocardiograms were corrected for errors in standardization. Bazett's formula $K = \frac{\text{Systole}}{\sqrt{\text{R-R}}}$ was used for calculating electrical systole. To determine heart rate, height of P, P-R interval, and, in Lead IV F, the height of T, six to ten complexes were measured and the results averaged. The areas of the QRS and T waves in Leads I, II, and III were measured from photographically enlarged records[13] and/or with a ×10 ocular[14] from the original records. The desired vectors were then obtained from a modified Dieuade chart. In one instance (Case 1) Leads I and III were taken simultaneously. The definition of symbols used in this paper are as follows:

A represents net area of the QRS, T, or QRS-T complex.
$\hat{A}$ represents the vector QRS, T, or QRS-T, representing both magnitude and direction.
G and $\hat{A}G$ = manifest area of QRS-T, and magnitude and direction of QRS-T, respectively.
$\hat{A}G$ and $\hat{A}_{QRS\text{-}T}$ are referred to as the ventricular gradient.
m.v.s. = microvolt-seconds.

RESULTS

Heart Rate.—The control rates varied from 58 to 75 in eight patients; in one patient (Case 3) the rate was 102 per minute. These were unchanged during the prodrome. In three instances at the onset of the chill phase sinus bradycardia was observed. After the onset of fever late in the chill phase, and in the flush phase, an average rise in pulse rate of ten beats per minute per degree Fahrenheit rise in body temperature occurred. In defervescence the average increase in cardiac rate above the control was 7.7 beats per minute per degree Fahrenheit elevation in body temperature.

P Wave and P-R Interval.—The control P-R intervals varied from 0.15 to 0.18 second, and the height and form of the P waves were normal. No significant changes were observed during any of the febrile phases.

The Relative Duration of Electrical Systole.—The control values for K varied from .390 to .408 in eight patients. In Case 3 the control value for K was .425. No changes were observed during the prodrome. In the chill phase, in all instances except Case 7, the value for K was increased. During the flush phase K

was increased in all instances as compared to the control, but was variable as compared with the chill, being unchanged in three, increased in five, and decreased in two instances (Table I). The greatest increase in K was from .400 to .447 (Case 1). In defervescence the value for K showed a return toward the control in all instances.

T Wave in Lead IVF.—No changes were observed during the prodrome. In the chill phase a decrease in the height of the T wave was observed in six of eight instances, ranging from 2 to 3 millimeters. In one instance (Case 8) the T wave during the chill phase was biphasic. Changes in the S-T segment during the chill phase were slight, the maximum being a depression of 0.5 millimeters. These changes were still present in the flush and defervescence phases (Fig. 1).

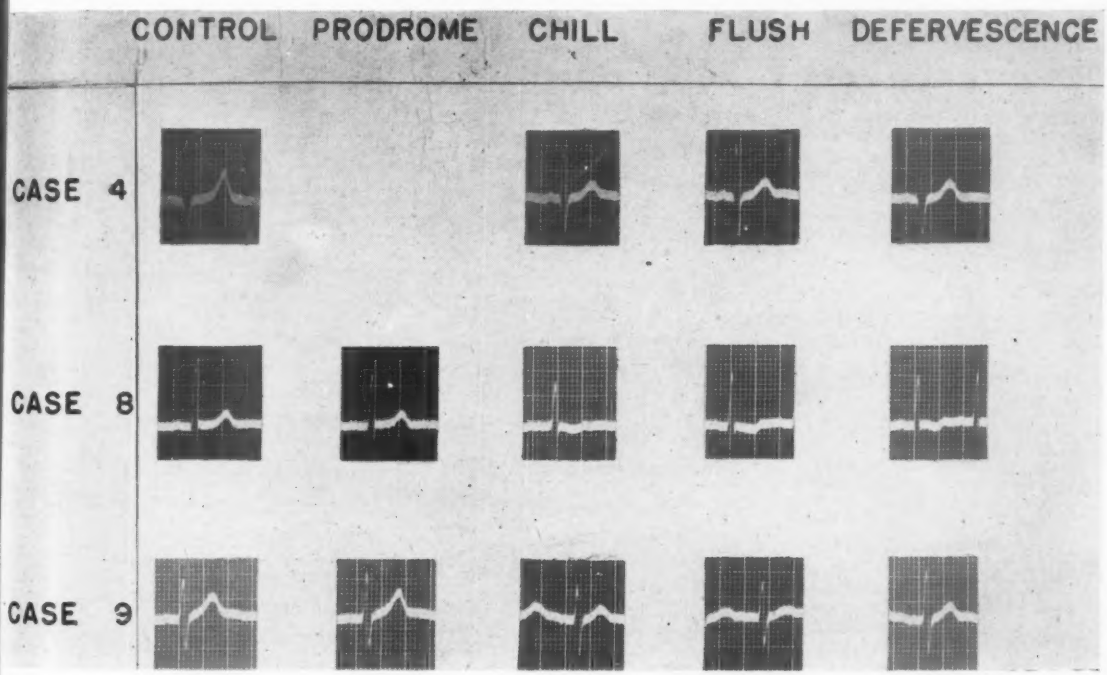

Fig. 1.—Lead IVF obtained during the various phases of a febrile reaction. In Case 4 the T wave is decreased in height during the chill, flush, and defervescence phases. In Case 8 slight depression of the S-T segment and a biphasic T wave are present in the chill and flush phases. The S-T segment is isoelectric in defervescence. In Case 9 the T wave is decreased in height in the flush as compared with the chill phase; a return toward the control is present during defervescence.

The Manifest Net Area and Direction of QRS-$\hat{A}_{QRS}$.—The control $\hat{A}_{QRS}$ varied from +20° to +69° in eight patients. It pointed to the left of $\hat{A}_G$ in four and to the right in four instances, the extremes being 3° to 17° in the former and 5° to 34° in the latter instances (Table I, Fig. 2). No changes were observed during the prodrome. The change in direction of $\hat{A}_{QRS}$ during the chill phase was slight (Table I, Fig. 2). Compared with the control and chill phase, there

were no changes during the flush phase except in Case 9, in which there occurred a rotation of 43 degrees to the left from its position in the chill phase (Table I, Fig. 2). The control A_{QRS} varied from 8 microvolt-seconds to 39 microvolt-seconds. This value decreased in the chill phase 5 to 15 microvolt-seconds in five cases and increased 3 to 4 microvolt-seconds in three cases. In the flush phase, as compared with the chill phase, A_{QRS} decreased in all instances, except Case 2, from 3.0 to 10.0 microvolt-seconds, the average being 5.7 microvolt-seconds. The average percentile decrease was 32.7. A_{QRS} showed a return to or toward the control values in all instances during defervescence.

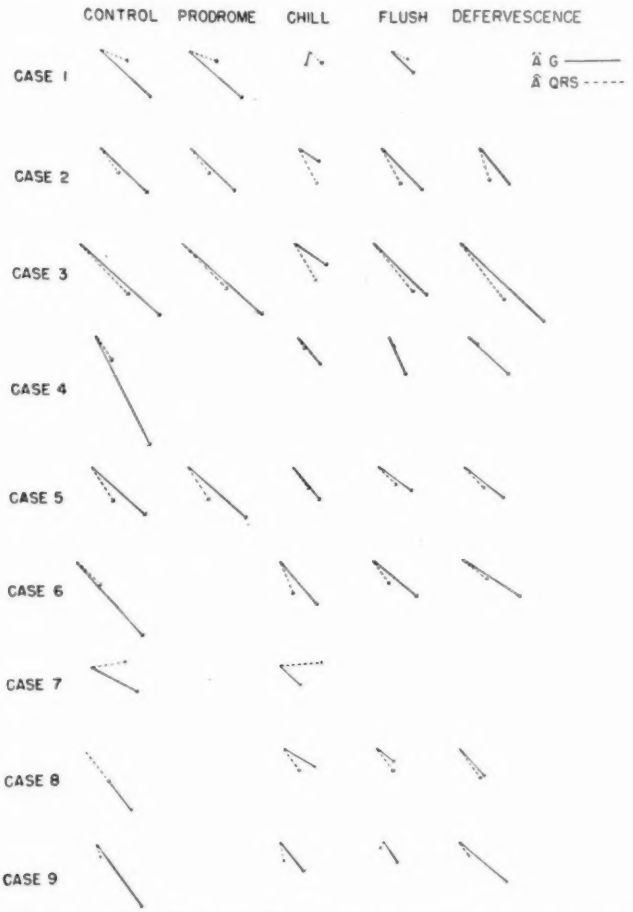

Fig. 2.—The relation between $\hat{A}_{QRS}$ and $\hat{A}_G$ during the various phases of a febrile reaction.

The Manifest Net Area and Direction of T-$\hat{A}_T$.—The control values for $\hat{A}_T$ varied from 17 to 48.5 microvolt-seconds and +20° to +64°. No changes were observed during the prodrome. There was a decrease in magnitude and a change in direction of $\hat{A}_T$ in all instances in the chill phase, represented in the electrocardiogram by a decrease in the height of T waves and/or a depression of the S-T segment (Table I and Figs. 3,*C* and *D*, 4*B*, and 5). Minor alterations

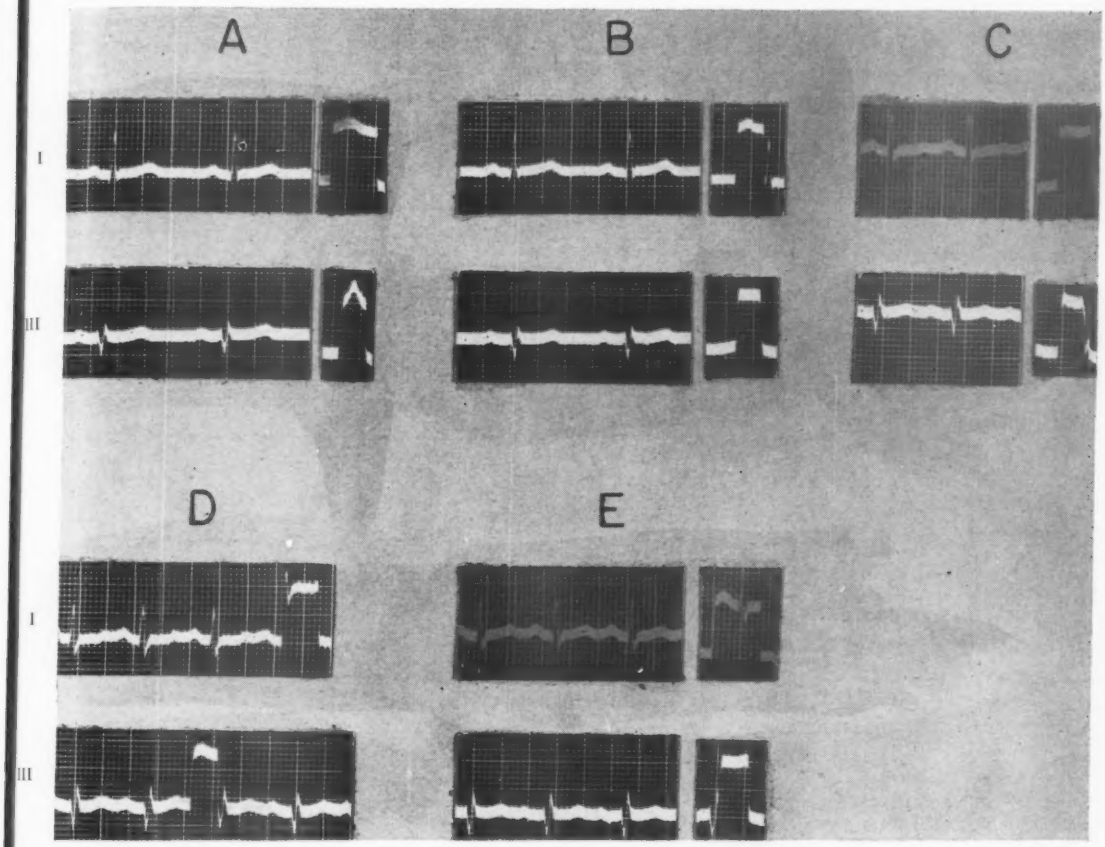

Fig. 3.—The electrocardiogram in Case 1. Leads I and III were taken simultaneously. *A*, control; *B*, prodrome; *C*, moderate chill phase; *D*, late chill phase; and *E*, flush phase.

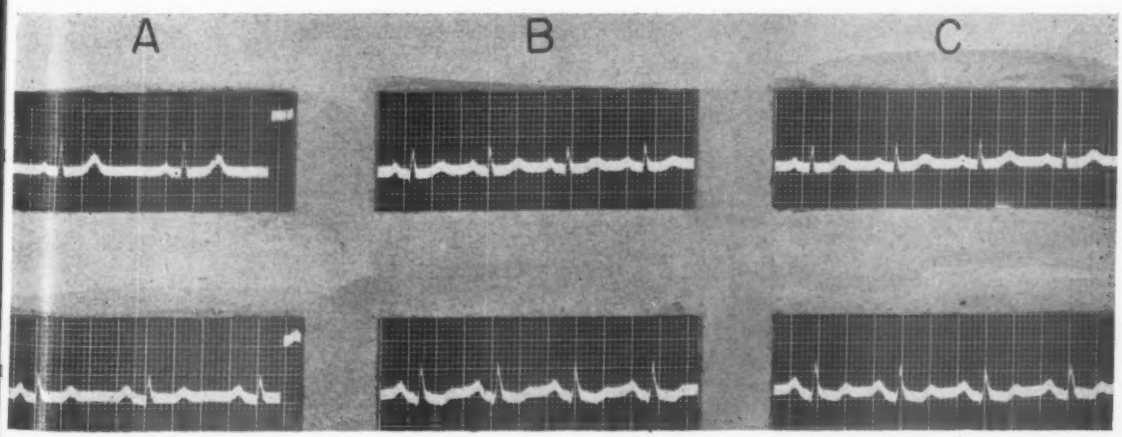

Fig. 4.—The electrocardiogram in Case 2 during a febrile episode. *A*, control; *B*, chill phase; and *C*, flush phase.

TABLE I. MEASUREMENTS OF THE CARDIAC RATE RELATIVE DURATION OF ELECTRICAL SYSTOLE AND THE VENTRICULAR GRADIENT IN FEVER INDUCED BY TYPHOID VACCINE

CASE	RATE PER MIN.	K $\frac{K = QT}{\sqrt{R\text{-}R}}$	$\hat{A}_{QRS}$		$\hat{A}_T$		$\hat{A}_G$		CHANGE IN A_{QRS} (PER CENT)	CHANGE IN G (PER CENT)	CHANGE IN RATE (PER CENT)	TEMP. °F.	REMARKS
			M.V.S.	DEGREE	M.V.S.	DEGREE	M.V.S.	DEGREE					
1	70	.406	17.0	+20	21.0	+55	38.0	+40	——	——	——	98.6	Control
	73	.400	17.0	+17	23.0	+51	39.0	+38	——	+ 2.6	+ 4.3	98.6	Prodrome
	107	.427	12.0	+21	2.0	+129	12.0	+32	−29.4	−68.5	+53.	100.4	Mod. chill
	118	.447	9.0	+42	8.0	+180	8.0	+108	−47.0	−79.0	+68.5	102.0	Late chill
	111	.434	11.0	+24	6.0	+60	16.5	+39	−35.2	−56.5	+58.6	103.5	Flush
2	73	.407	18.0	+50	17.0	+35	35.0	+42	——	——	——	98.2	Control
	72	.407	18.0	+50			35.5	+42				98.2	Prodrome
	107	.415	22.0	+60	12.0	−70	14.5	+30	+22.2	−58.5	+46.5	101.0	Chill
	109	.415	23.5	+60	9.0	− 5	32.0	+45	−30.6	− 8.6	+49.2	102.4	Flush
	97	.407	19.0	+70	11.0	+10	27.0	+50	+ 5.5	−22.8	+32.8	101.2	Defervescence
3	102	.425	39.0	+43	21.5	+35	60.0	+40	——	——	——	99	Control
	102	.425	38.0	+43			60.0	+40	——	——	——	99	Prodrome
	116	.445	24.0	+57	9.5	−65	21.0	+32	−38.4	−65.	+13.7	104	Chill
	136	.450	36.0	+48	6.0	−10	42.0	+43	− 8	−30	+33	105.2	Flush
	110	.435	40.0	+50	23.5	−29	64.0	+42	+ 2.6	+ 7	+ 7.8	102.5	Defervescence
4	58	.408	17.0	+55	48.5	+63	66.0	+61	——	——	——	98.0	Control
	96	.407	8.0	+55	13.0	+42	20.0	+49	−53	−70	+65.5	101.2	Chill
	98	.417	7.0	+60	15.0	+61	23.0	+62	−59	−65	+69	102.0	Flush
	83	.410	8.0	+37	22.0	+41	30.0	+40	−53	−54.5	+43	101.6	Defervescence
5	68	.405	23.0	+55	19.0	+20	42.0	+40	——	——	——	98.5	Control
	68	.405	22.0	+55			44.0	+40				98.5	Prodrome
	82	.407	16.0	+50	7.0	+40	23.0	+48	−30	−45	+21	101.2	Chill
	88	.413	15.0	+43	8.5	+14	23.0	+34	−35	−45	+29	102.3	Flush
	95	.402	17.0	+42	10.0	+28	27.0	+37	−26	−36	+40	101.6	Defervescence

6	62	.408	19.0	+41	37.0	+47	56.0	+46	——	——	——	97.9	Control
	86	.418	20.0	+65	13.0	+17	32.0	+47	+ 5	−43	+39	101.0	Chill
	88	.412	15.5	+52	17.0	+17	32.0	+38	−18	−43	+42	101.7	Flush
	82	.406	19.0	+35	20.0	+31	39.0	+31		−30	+32	100.6	Defervescence
7	65	.405	20.0	−9	17.0	+64	29.0	+25	——	——		98	Control
	107	.400	24.0	−5	14.0	+140	16.0	+40	+20	−45	+65	103.7	Chill
8	74	.390	21.0	+51	20.0	+53	41.0	+51				99.0	Control
	76	.403	16.0	+52	8.0	−19	21.0	+30	−23.8	−49	+3	99.6	Early chill
	113	.416	16.0	+51	5.0	−90	13.0	+36	−23.8	−68	+53	103.8	Flush
	113	.411	21.0	+51	1.0	−31	21.0	+46		−49	+53	102.0	Defervescence
Effect of Oxygen 8a	61	.400	17.0	+50	21.0	+59	37.5	+59				99.0	Control
	97	.412	16.0	+49	9.0	−90	11.0	+14	− 6	−71	+59	101.7	Late chill
	100	.412	16.0	+53	9.0	−76	11.5	+15	− 6	−70	+64	103.3	Flush
	95	.390	16.0	+46	6.0	+46	22.0	+46	− 6	−41	+56	102.0	Defervescence
9	75	.392	8.0	+69	35.0	+48	43.0	+52	——			98.2	Control
	107	.408	11.0	+75	11.0	+20	21.0	+49	+38	−51	+43	101.0	Chill
	125	.412	4.0	+118	11.0	+37	14.0	+55	−50	−68	+67	102.4	Flush
	105	.397	10.5	+48	16.0	+30	25.5	+38	+31	−41	+40	101.4	Defervescence
Effect of Oxygen 9a	70	.390	7.0	+50	46.0	+60	53.0	+60	——	——	——	98.6	Control
	98	.413	6.0	+36	18.0	+35	23.0	+35	−14	−57	+40	101.0	Chill
	100	.438	4.0	+59	25.0	+59	29.0	+60	−43	−45	+43	102.4	Flush
	75	.407	11.5	+45	26.0	+42	38.0	+45	+64	−28	+ 7	100.2	Late defervescence

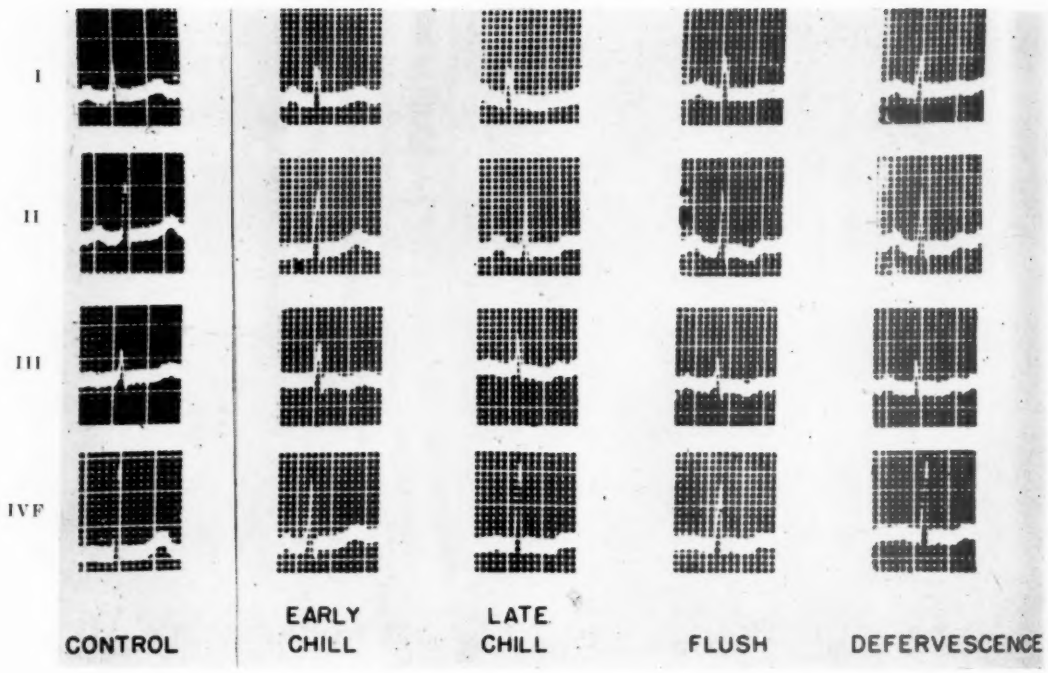

Fig. 5.—The electrocardiogram in Case 8 during the various phases of a febrile episode. T wave and S-T segment changes are present in the limb leads and Lead IVF in the chill and flush phases. A return toward the control is seen in defervescence.

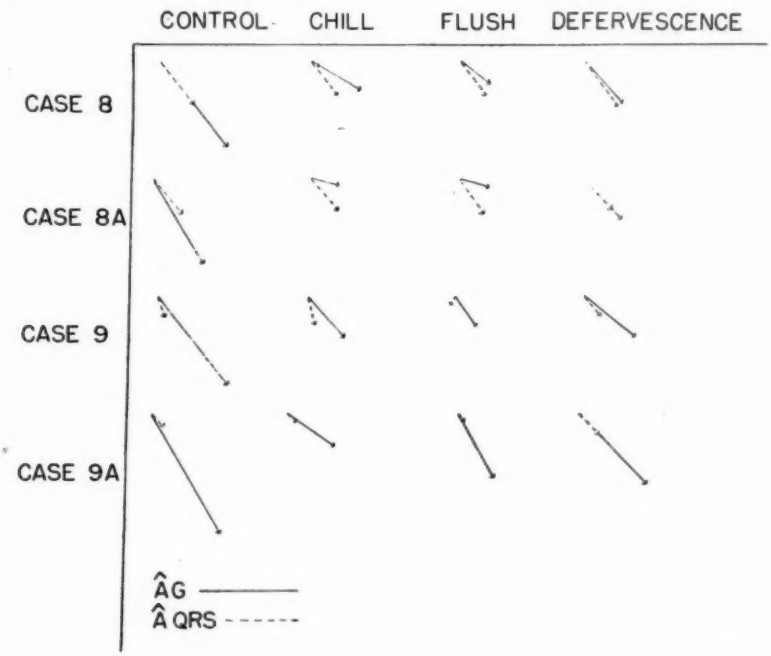

Fig. 6.—The effect of the administration of 100 per cent oxygen on the relation between $\hat{A}_{QRS}$ and $\hat{A}G$.

in ÂT were present in the flush phase as compared with the chill phase. Marked alterations in the direction of ÂT occurred in the flush phase as compared to the chill in four instances (Table I). In all instances but one, ÂT increased during defervescence, represented in the electrocardiogram by an increase in the size of the T waves and/or a rise in the level of the S-T segment (Table I, Fig. 5).

ÂG.—The control ÂG varied from 29 to 66 microvolt-seconds and +25° to +61°. No change was observed in the prodrome. In the chill phase there was a decrease in AG in every instance, varying from 13 to 39 microvolt-seconds, and averaging 25.5, or 55 per cent. In the flush phase in seven cases there were no significant changes compared with the chill phase. When compared with the control, G was smaller by 18 to 43 microvolt-seconds (average 26.5 or 48 per cent). In Case 2 a return to the control value was observed. G was increased in six of the seven cases in defervescence as compared with the flush phase (Table I). In five instances it had not yet returned to the control values (Table I). Minor changes in direction during the chill were present in almost every instance. In one patient (Case 1) a marked rotation of approximately 70° to the left was present (Figs. 2 and 3,*C* and *D*). During the flush phase no additional significant shift was observed except in Case 1, in which return toward the control direction occurred (Figs. 2 and 3,*E*). During defervescence the direction of ÂG showed small rotational differences as compared with the control and flush phases.

The Effect of Oxygen.—In the two patients (Cases 8a and 9a) who were given oxygen continuously, the increase in the pulse rate was not as great as when oxygen was not administered. No differences in the values of K, AQRS, ÂT or AG were observed (Table I). The direction of ÂG in Case 8 during administration of

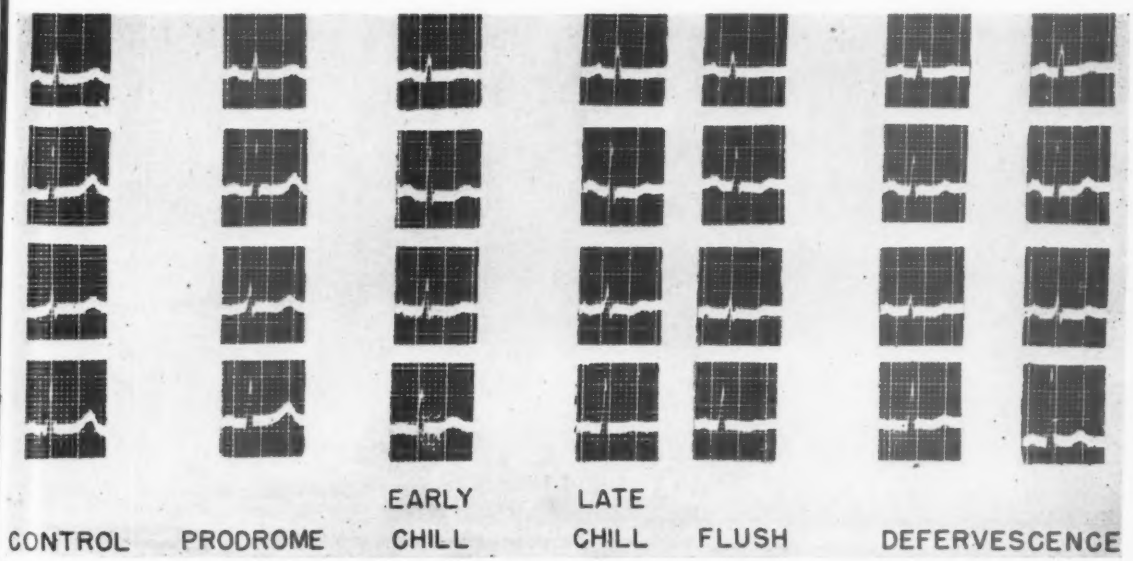

Fig. 7.—The electrocardiogram in Case 8a showing the effect of continuous oxygen administration during a febrile episode. This figure is to be compared with Fig. 5.

oxygen showed a more marked rotation to the right during the chill and flush phases (Fig. 6), and the electrocardiogram showed more marked T-wave inversion and S-T segment depression (Figs. 5 and 7).

COMMENT

The changes observed during fever include not only the effect of heating the heart but also the influence of concomitant physiologic factors,[12] such as cardiac rate, cardiac output, anoxia, hyperventilation, and accumulation of blood metabolites.

Cardiac Rate.—A 50 per cent increase in cardiac rate results in a decrease in G of approximately 39 per cent.[15,16] It might be expected, therefore, that multiplication of net QRS-T area in microvolt-seconds by the cardiac rate per miuute would show an increase in the size of G per minute. It is apparent that this does not occur (Table I). It is further clear that no correlation exists between the per cent increase in rate and the per cent decrease in G (Table I). Thus, in two instances (Cases 3 and 8) with a slight change in rate, a marked decrease in the size of AG occurred during the chill phase. Furthermore, shifts in the direction of ÂG should not occur with simple rate changes; such a shift was observed in Cases 1 and 8.

Cardiac Stroke and Minute Volume Output.—It has been suggested[15] that changes in stroke output may cause a change in G and that an increased stroke volume is associated with a large gradient, and vice versa. Ashman[16] attributed the increase in G during fever to increased stroke output. Previous studies,[12] however, have shown no striking changes in stroke output during fever induced by typhoid vaccine. Although the cardiac minute volume output may either rise or fall during the chill phase, it invariably increases markedly in the flush phase. If the changes in ÂG were related to minute volume output, they would be opposite in the chill and flush phases; it is apparent that this is not the case (Table I).

Hyperventilation.—The electrocardiographic changes observed in hyperventilation are characterized by inversion of T waves, and S-T segment depression.[17] Calculation of the QRS and T-wave areas of electrocardiograms published in Thompson's paper[17] is presented in Table II and Fig. 8 and shows that a de-

TABLE II. VENTRICULAR GRADIENT IN HYPERVENTILATION

	RATE	ÂQRS		ÂG		PER CENT INCREASE IN RATE	PER CENT INCREASE IN G
		M.V.S.	DEGREE	M.V.S.	DEGREE		
Control	77–60	41	−78	47	−75		
After hyperventilating	87	26.5	−72	25	−84	45	47

crease in the size of the gradient, assuming correct standardization, may occur after hyperventilation. In the leads used for the calculation, the control electrocardiogram shows a difference in rate of 77 and 60 beats per minute. The rate after hyperventilation is increased 45 per cent over the lower rate, while the gradient is decreased 47 per cent. There is a slight rotation of $\hat{A}G$ to the left, and a simultaneous slight shift of $\hat{A}_{QRS}$ to the right. This change, therefore, is similar to those observed by us in some instances in fever (Table I, Fig. 2). Our previously published data[12] show that alkalosis occurs in the chill and flush phases and while alkalosis may be responsible for the changes in gradient observed, it may not be valid to make this interpretation since measurements of blood pH[18] were not made simultaneously with recording of the electrocardiogram.

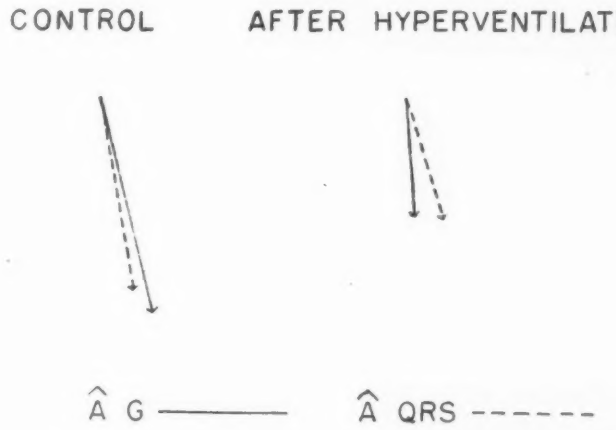

Fig. 8.—The relation between $\hat{A}_{QRS}$ and $\hat{A}G$ in hyperventilation.

The value for K is most markedly increased in the flush phase suggesting that alkalosis is most severe at this time. The directional change in $\hat{A}G$, on the other hand, is less marked in the flush phase and in several instances $\hat{A}G$ returned to the control level in this phase while K was still increased (Table I). It is of interest that, recently in a group of patients with acute glomerulonephritis, La Due and Ashman[19] found a rightward deviation of $\hat{A}G$ associated with decreased height and inverted T waves in Lead I and an increased height of the T wave in Lead III. In this group of patients the duration of the Q-T interval was longer than that observed when no gradient change was demonstrated.

Changes in the Myocardium Due to Local Effects of Heating.—In physically induced fever T-wave inversion and S-T segment changes occur.[9,10,20] No analysis of the ventricular gradient under these circumstances has been found in the literature. It is apparent from the present study that the temperature within the myocardium cannot be an important factor in causing the observed changes, for the gradient returns toward the control in the flush phase (Cases 1, 2, and 3).

Anoxia.—In our previous studies no evidence of arterial oxygen unsaturation was noted in any phase of fever. A lowered venous oxygen content occurs in the chill phase but is not present in the flush phase. The persistence of the electrocardiographic changes in the flush phase would negate anoxia as the sole cause of these changes. Furthermore, a more marked shift in the ventricular gradient to the left occurred in Case 8 while oxygen was being administered.

Increase in Metabolites in Blood.—Unpublished data[21] show progressive rises in blood pyruvate and lactate during the febrile episode. While it is not known whether similar increases in other tissue metabolites occur, it is clear that the observed changes in the ventricular gradient do not parallel the blood chemical changes.

Significance of the Observed Changes.—Analysis of the ventricular gradient affords a better understanding of the commonly observed T wave and S-T segment changes associated with fever. In approximately half of the cases, the occurrence of these changes is explained by a change in the position of the heart and/or an increased heart rate. In the remaining cases the T wave and S-T segment changes are primary, indicating physiologic alterations in the myocardium of unknown origin. The decreased magnitude of the gradient without change in its direction is not unlike that seen after digitalis administration,[16] and is therefore not necessarily an indication of a deleterious change in the myocardium.

SUMMARY AND CONCLUSIONS

1. The electrocardiographic changes observed during fever induced by the intravenous injection of typhoid vaccine in man have been studied. The three standard limb leads and Lead IV F were recorded in the control, prodromal, chill, flush, and defervescent periods of the febrile reaction. The QRS and T-wave areas, the duration of electrical systole corrected for rate, and the P wave and P-R interval were studied.

2. No significant changes were observed during the prodrome.

3. The heart rate increased approximately ten beats per minute per degree Fahrenheit rise in body temperature. In three patients, at the onset of the chill phase, a slight to moderate decrease in the heart rate was observed.

4. No significant changes in the height or duration of the P wave, or in the P-R interval, were observed in any of the phases.

5. In eight of nine patients, an increase in K was observed in the chill and flush phases with a return toward the control value in defervescence. This may be attributed to alkalosis which occurs in fever.

6. The height of the T wave in Lead IVF decreased in the chill phase and remained so in the flush and defervescence phases.

7. In all patients a decrease in the magnitude of the ventricular gradient was observed in the chill phase. This was manifested in the electrocardiogram by a decreased height or inversion of the T wave and depression of the S-T segment. During the flush phase in two of nine patients partial return toward

the control values occurred, but in the remaining patients this did not occur until defervescence. There was no uniform change in direction of the ventricular gradient during any of the phases. Two instances of pronounced shift of ÂG, one toward the left, the other toward the right, were observed. In the latter a more marked shift was observed while oxygen was being administered.

8. The decrease in the magnitude and the change in direction of ÂG without a corresponding change in $Â_{QRS}$ in some cases are interpreted as signifying that the observed T wave and S-T segment changes in fever are primary. They denote the existence of definite but reversible changes in the myocardium of unknown origin and significance.

9. In the remaining cases the T wave and S-T segment changes can be explained by a change in the position of the heart and/or increased heart rate.

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Clinical Reports

SECONDARY HYPERTROPHIC OSTEOARTHROPATHY IN CONGENITAL HEART DISEASE

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SINCE the early descriptions of secondary osteoarthropathy by von Bamberger and by Marie, there have been numerous and divergent opinions as to its etiology. The role of chronic pulmonary diseases, including bronchiectasis, tuberculosis, empyema, abscess, malignancy, and other conditions producing extensive proliferation of interstitial tissue in the lungs, have been considered essential factors in its development. In this country, Thayer[15] reported several cases of secondary pulmonary osteoarthropathy and differentiated its features from those of acromegaly. In 1903, Janeway[7] reviewed the subject, adding cases of his own, and commented on the rarity of the condition. Landis[9] described his findings in two cases associated with old tuberculous lesions and in his discussion stated that of 109 recognized cases only nine had been found in the United States. Brooks,[3] in discussing the etiology of secondary osteoarthropathy, expressed his belief that long standing disease of the lungs was the principal cause. Kessell,[8] in an investigation of thirty-two cases of pulmonary tuberculosis with clubbed fingers, found significant bone changes in ten of his patients. In a recent study of the circulation in clubbed fingers, Charr and Swenson[4] reported six cases showing increased vascularity, but osteoarthropathy was not discussed. Five of their patients had chronic pulmonary disease, but one was a young man of 25 with a congenital cardiac defect and it is possible that a careful study of the long bones might have revealed some of the changes associated with osteoarthropathy.

In a comprehensive review of the subject in 1915, Locke[10] analyzed 144 cases and ascribed six to heart disease but only two to congenital lesions. In addition to the original case described by von Bamberger, there has been reported the well-authenticated case of Shaw and Cooper[13] in a patient with congenital heart disease, and another by Thorburn[16] in a patient with a valvular defect of uncertain origin.

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It is significant that by far the greater number of reported cases of osteoarthropathy have occurred in connection with pulmonary lesions, whereas the only successful reproduction of the characteristic bone lesions in animals was secured by Mendlowitz and Leslie[12] who established an artificial communication between the pulmonary artery and the left auricle in a dog, duplicating as nearly as possible the oxygen unsaturation present in congenital malformations of the heart with cyanosis. An autopsy eight months later showed the changes typical of hypertrophic osteoarthropathy.

The case which we describe gives no history, physical signs, nor roentgenologic signs of pulmonary disease, but presents the classical picture of the tetralogy of Fallot, with cyanosis, polycythemia, bulbous fingers and toes, soft tissue deformities about the wrists and ankles, and roentgenologic evidence of a hypertrophic osteoarthropathy.

CLINICAL REPORT

L. S., 26 years of age, a bookkeeper, was born a "blue baby," and had been cyanotic during his entire life. There is no history of heart trouble or of any congenital defects in his family. His childhood was uneventful and he escaped the usual childhood diseases. Deformities of the wrists and ankles were first noticed at the age of 12 years. During adolescence he had periodic pain in the wrists and ankles and at the age of 15 years he had an attack of "flu"; at no other time were these joint pains accompanied by fever. He completed a high school education, but was not able to engage in any occupation or recreation which required physical exertion.

The patient was first examined at the Toledo Clinic in January, 1946. There was a moderate general cyanosis which was most conspicuous in the hands and feet. The fingers and toes showed marked clubbing and there were soft irregular swellings about the wrists and ankles (Figs. 1 and 2). The hands presented the clawlike appearance mentioned by early writers. The lower legs suggested the "elephant foot" described by von Bamberger in one of his cases. There was no tenderness to pressure nor was there pain on manipulation of the joints. Finger- and toenails were unusually broad in proportion to the width of the digits. There were patches of dark purple discoloration on the lower extremities. Body development was normal. There was nothing to indicate acromegaly. The chest was of normal shape and expansion was equal. The respiratory sounds were normal and there were no findings which indicated any chronic pulmonary disease. The heart was not appreciably enlarged, but the width of manubrial dullness was increased. On palpation a double systolic impulse was felt over the precordium and was visible in the vessels of the neck. On auscultation a loud systolic murmur was heard, maximum in the fourth and fifth intercostal spaces to the left of the sternum. This murmur was transmitted to the right rather than to the left. Another systolic murmur of higher pitch and different quality could be heard in the second left intercostal space, but was not accompanied by the thrill usually found in pulmonary stenosis. No diastolic murmurs could be discovered. The second sound was louder to the left than to the right of the sternum. The pulse was of regular rhythm with a rate of 88 per minute. The brachial pressure was 124/86, and the systolic pressure in the lower extremity was 140 by palpation.

There was a compensatory polycythemia with an erythrocyte count of 7,260,000 and a hemoglobin reading of over 140 per cent. The leucocytes numbered 6,550 with a normal differential count. The sedimentation rate was normal. Kahn and Wassermann tests were negative.

The electrocardiogram (Fig. 3) showed a normal sinus rhythm and a rate of 84 per minute. The P-R interval measured 0.20 second; the QRS interval, 0.08 second. There was a definite right ventricular preponderance. The auricular complexes were unusually high in Leads I and II. Special unipolar parasternal leads showed large diphasic auricular waves in the second, third, and fourth intercostal spaces to the right of the sternum. The character of auricular waves of

this type showing an abrupt intrinsic deflection suggested the proximity of the auricular wall to the parasternal electrodes, and located the right auricle somewhat to the right and above its usual position.

The clinical diagnosis, based on the history, physical examination, and electrocardiographic findings, was that of congenital heart disease of the Fallot type.

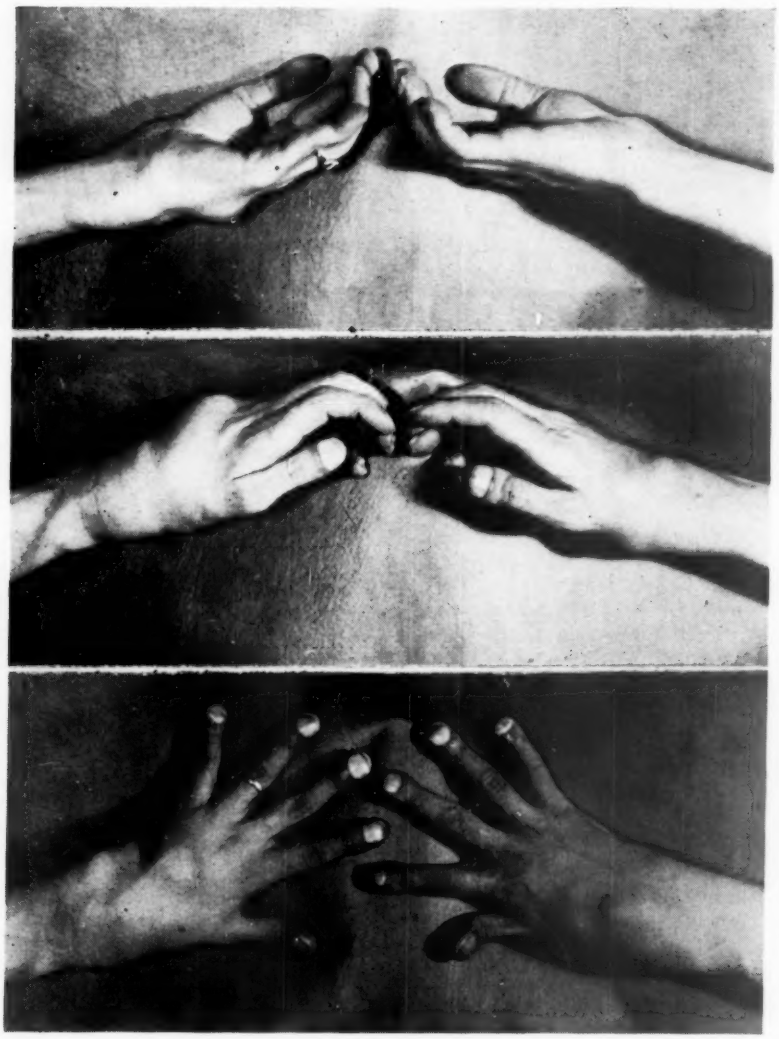

Fig. 1.—Dorsal and lateral views of the hands, showing the clubbed fingers, broad arched fingernails, deep cyanosis of the finger tips, the spindleshaped joints, the irregular swellings over the carpals and metacarpals, and the clawlike position of the fingers.

Fig. 2.—Lower extremities, showing clubbing of the toes, irregular swellings about the ankles, cyanotic areas on the feet, and the diffuse exanthematous rash on the lower anterior portion of the leg.

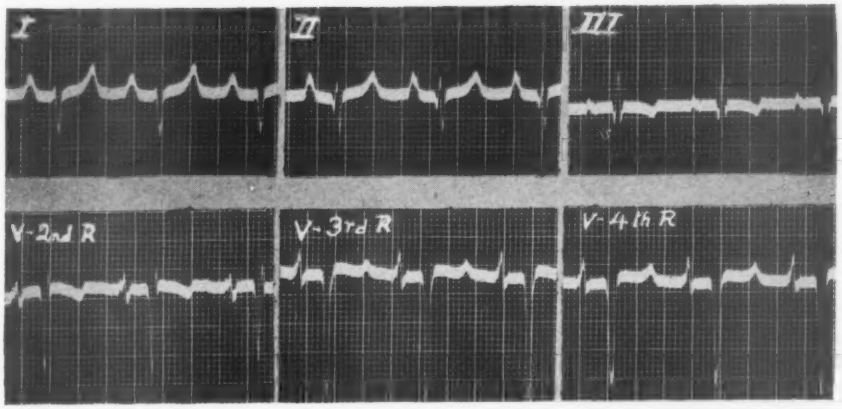

Fig. 3.—*Upper:* Standard leads. Right ventricular preponderance. Unusually large auricular waves in Leads I and II.

Lower: Unipolar parasternal leads from the second, third and fourth intercostal spaces to the right of the sternum show the abrupt intrinsic deflection in the P waves characteristic of direct leads from the auricular wall. The presence of these waves suggests the juxtaposition of the right auricle with the chest wall directly beneath the exploring electrode. Intrinsic deflections were not found to the left of the sternum.

Roentgenologic Discussion.—In the case under consideration, it is noteworthy that our roentgenograms failed to disclose any evidence of the usually purported etiological diseases of the pleura, lungs, mediastinum, or spine to account for the osseous and soft tissue changes in the extremities. Recognition of this fact immediately places this patient in a category of unusual interest; that of hypertrophic osteoarthropathy in uncomplicated congenital heart disease.

In the frontal plane view (Fig. 4) the cardiac silhouette does not appear to be definitely enlarged, although its area, when calculated according to the method of Hodges and Eyster,[6] yields a 14 per cent increase over that predicted. The often described characteristic "coeur en sabot" configuration of right ventricular hypertrophy is somewhat modified by submergence of a portion of the heart shadow below that of the diaphragm. At the screen with the patient turned to the left oblique position an impression of right ventricular enlargement is obtained. Moreover, the right cardiac contour is rather prominent, suggesting a lateral displacement of the right auricle by hypertrophy of the right ventricle.

Of diagnostic significance is the complete absence of all signs pointing to enlargement of the outflow tract of the right ventricle. In addition to the slight reduction of the normal "waistline," the aortic window, as viewed in the left anterior oblique position, is easily recognized (Fig. 5).

By far the most conspicuous feature is the prominence of the right vascular contour which fluoroscopically shows an increased amplitude of pulsation. The aortic knob shows a synchronous thrust. In Fig. 5, the ascending and transverse aortic shadow appears large. This observation is in keeping with the enlargement of the ascending aorta described by White and Sprague[17] in autopsy protocols of adults with the tetralogy of Fallot. Only as the hemodynamics are altered by it does the dextroposed aortic orifice itself participate in these morphologic changes.

Somewhat contrary to the concept of pulmonary circulatory deficiency in the tetralogy of Fallot, as expressed by Blalock and Taussig[1] and reflected in roentgenograms by the absence of prominent vascular markings, this patient does show evidence of increased lung vascularity. The changes are most pronounced in the peripheral zone of the lungs. The hilar shadows are also prominent, and upon close inspection and analysis disclose an unusual number of component parts.

In view of our patient's age and the absence of abnormal pulsations in the hilar vessels, coupled with the lack of other evidence of a patent ductus arteriosus, we believe these changes in the pulmonary circulation are largely secondary to the polycythemia and its concomitant increased plasma volume, operating over a long period of time and producing an ectasia of the pulmonary blood vessels. Another consideration which cannot be eliminated is the possible development of a collateral circulation between the systemic and the pulmonary circulations through small blood vessels, particularly in the hilar area.

The roentgenograms of the extremities (Figs. 6 and 7) disclose symmetrical hypertrophy of the radii, ulnae, tibii, and fibulae. The broadening of these bones is in sharp contrast to the relatively normal diameter of the carpus and tarsus and the more distal bones of the hands and feet. The radii and ulnae

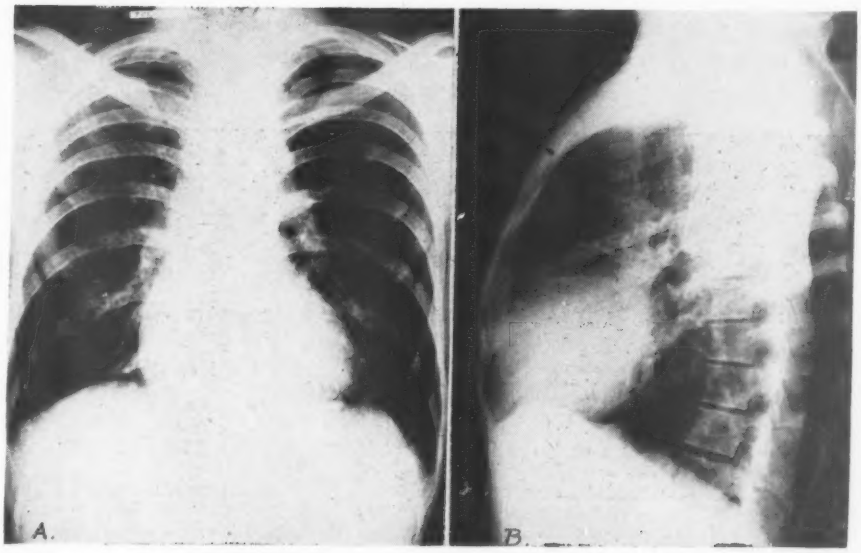

Fig. 4.—Roentgenograms of the chest. *A*, Frontal view shows a relatively narrow "waist" in contrast to the convexity seen in other congenital defects and acquired lesions. *B*, Lateral view shows an adequate retrocardiac space and an increase in the hilar shadows.

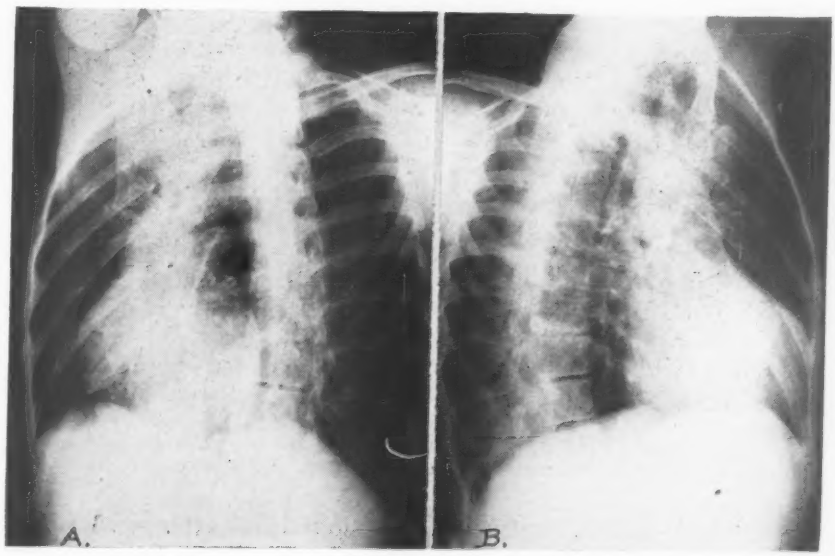

Fig. 5.—Roentgenograms of the chest. *A*, Left oblique view shows unusual clarity of the "aortic window." *B*, Right oblique view shows preservation of the retrosternal triangular space and a rather large ascending aorta.

show a well-differentiated cortex with only a slight roughening along the interosseous margins of the former. The lower tibia (Fig. 7), however, displays a very definite delineation between the ossifying periosteal new bone formation and a well-organized underlying cortex. At several points of tendon and ligament

Fig. 6.—Roentgenograms of the hands and feet present an interesting contrast between the terminal phalanges of the feet and those of the hands. The distal portions of the radius and ulna show an increased diameter. Soft tissue hyperplasia is evident.

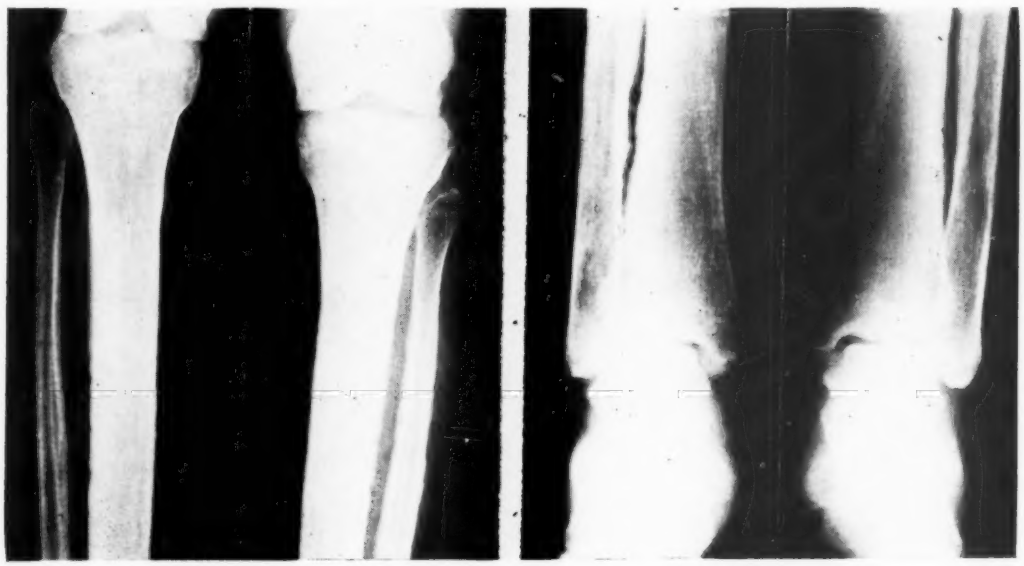

Fig. 7.—Roentgenograms of the lower legs show thickening of the tibial and fibular diaphyses and residual productive periosteal changes in the distal portion of the long bones.

insertion, notably at the radial styloids, the external tibial tuberosities, and the internal malleoli, there are osteophytic irregularities as well as hypertrophy.

A striking feature is the soft tissue hyperplasia of the wrists and ankle joints (Figs. 1 and 2), the production of which probably depends on the same factors which cause proliferation of the cambium layer of the periosteum. The soft

tissues about the terminal phalanges of all fingers and toes show the bulbous enlargement characteristic of clubbing. The tufted portion of the terminal phalanges of the fingers appears smooth, whereas that of the toes shows well-advanced bone resorption with a resulting sharpening and spinelike pointing of the tips (Fig. 6). This discrepancy between the upper and lower extremities suggests the possibility of a hypostatic etiological factor and supports the theory that an altered blood flow is at least an important adjunct, if not the primary cause. It is to be noted that similar osseous changes are found in Raynaud's and Buerger's diseases. Inferior to the external malleolus and anterior to the ankle joint there can be seen several circumscribed areas of finely granular density, which indicates a deposition of calcium salts in the thickened soft tissues which lie adjacent to and perhaps involve the joint capsules. No phleboliths or other signs suggesting angiomatous formations were found and no destruction of the articular cartilages could be demonstrated.

Subsequent Record.—On May 6 an anastomosis was established between the right common carotid and the right pulmonary arteries.* Notwithstanding the patient's age the result was satisfactory. Dyspnea was relieved and cyanosis could be recognized only on critical inspection. During the operation it was necessary to resect the right subclavian artery. Collateral blood vessels maintained an adequate circulation in the right arm. It was of particular interest to find that within six weeks the deformities about the hands and feet had become less conspicuous. The change was especially noticeable in the right hand which had lost its grotesque appearance and was almost normal in size and shape. Another finding of significance was the evidence, in chest films and by fluoroscopic examination, of the persistence of a vascular increase in the right lung, while the left lung appeared relatively normal. The erythrocyte count had fallen to 6,000,000 and the hemoglobin to 120 per cent. It was estimated by Taussig[14] that oxygenation of the blood was doubled by the carotid-pulmonary anastomosis. Our recent examination indicates that this increase in pulmonary circulation is preponderantly within the right lung.

COMMENTS

The presence of large, soft, irregular swellings about the wrists and ankles, as illustrated in Figs. 1 and 2, gives rise to speculation as to their connection with the proliferative changes in the bones and periosteum. Thayer[15] describes similar conditions in his report on secondary pulmonary osteoarthropathy and states: "Effusions into the joints are common, the joints most commonly affected being those nearest the bony changes, as the ankle, wrist and elbow. Enlargement of the lower part of the forearm accompanies the changes in the hands. . . . In some cases the enlargement is due entirely to hypertrophy of the soft tissues. Analogous changes take place in the feet and legs." Janeway[7] in his description of the findings in a man, 22 years of age, with chronic suppurative bronchiectasis and secondary osteoarthropathy, states that "One was struck with the tremendous size of the hands and feet . . . the lower third of leg and arm were much enlarged so that both had a straight line from knee and elbow to ankle and wrist." Thorburn[16] also mentions "Excessive fluid in the joints and some erosion of the cartilages." The illustrations attached to the descriptions by Thayer and Janeway present a striking resemblance to those of the case

*By Dr. A. Blalock, Baltimore, Md.

which we present. Wissing and Weisz[18] discovered progressive hypertrophic bone changes in a dog with pulmonary carcinomatosis. Soft tissue swellings were noted on both fore and hind legs. Autopsy showed the bone lesions and the periosteal proliferation of secondary osteoarthropathy and also considerable hyperplasia of the connective tissues.

It has been suggested that these soft tissue deformities about the ankles and wrists should be regarded as due to independent, coexisting congenital defects in the tendon sheaths or to congenital cystic hygromata. In view of the fact that deformities of this character have been so frequently reported in the secondary osteoarthropathy of acquired pulmonary disorders, it seems unnecessary to assume the presence of additional, unrelated congenital defects. It is more reasonable to consider them as associated with the proliferative and degenerative changes in the bones and periosteum and due to the same etiological factors. It is significant that these soft tissue deformities are in close proximity to the bone lesions and are not found in other localities. As with osteoarthropathy they are found in the most dependent portions of the extremities which in itself points to the influence of peripheral stasis.

The postoperative changes in the soft tissues of the extremities show that some of the conditions associated with secondary osteoarthropathy are reversible and lend support to the view that the dynamics of the circulation have a part in producing the soft tissue deformities. The fact that local improvement was most marked in the arm which had been deprived of its normal blood supply furnishes additional evidence that increased vascularity and peripheral stasis contribute to the soft tissue hyperplasia and probably also to the characteristic changes of secondary osteoarthropathy.

That these changes are most commonly associated with chronic pulmonary disease is evident from the analytical reports of Locke[10] and a more recent review of the entire subject by Mendlowitz,[11] and yet the occasional but well-proven cases of secondary hypertrophic osteoarthropathy developing late in the cyanotic group of patients with congenital cardiac defects must be conceded.

In view of the perfection of surgical procedures as developed by Gross[5] and Blalock and Taussig[1,2] it becomes of increasing importance for the clinician and the roentgenologist to recognize and identify the cardiac malformations amenable to early surgical treatment.

SUMMARY

A case of secondary hypertrophic osteoarthropathy associated with uncomplicated congenital heart disease of the Fallot type is presented, together with a roentgenologic study and with illustrations showing the gross physical deformities, electrocardiographic records, and x-ray findings. The etiology is discussed and evidence is given to show that increased vascularity and peripheral stasis are important contributing factors in the production of connective tissue hyperplasia, as well as of characteristic changes in bone and periosteum.

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ELECTROCARDIOGRAPHIC CHANGES RESULTING FROM ACUTE COCAINE INTOXICATION

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BECAUSE of the urgency of the situation and the frequent rapid demise of the patient, electrocardiographic observations during acute cocaine poisoning have not been reported. Although several investigators[1-4] have recorded graphically the effects of the cocaine group of drugs applied upon or injected into the hearts of experimental animals, search of the literature fails to reveal electrocardiograms obtained during the course of clinical cocaine or novocaine reactions. The following study is presented because a unique opportunity arose for clinical observation over a five and one-half hour period before the patient succumbed to acute cocaine intoxication.

REPORT OF CASE

A 20-year-old white man was admitted to the hospital for the purpose of a nasal submucous resection. The past history revealed no serious illnesses or previous operative procedures. Examination showed a moderately severe deviation of the nasal septum to the right. The heart was not enlarged, the sounds were of good quality, the rhythm was regular at a rate of 80 per minute, and there were no murmurs. The blood pressure was 108/66. The lungs and abdomen revealed no abnormalities. All laboratory data were normal.

The night before operation the patient received 1½ grains of nembutal. The following morning breakfast was withheld and at 9:00 A.M., ¼ grain of morphine sulfate and 1/100 grain of atropine sulfate were administered hypodermically. At 9:30 A.M., 1½ grains of nembutal were given by mouth. On arrival at the operating room the patient was in excellent condition and fully conscious. At 10:15 A.M., preparation for nasal surgery was begun. This consisted of intermittent spraying of small amounts of a solution of 20 per cent cocaine containing ten minims per ounce of 1/1000 epinephrine. Approximately 6.0 c.c. of this topical spray were used over a period of fifteen minutes. A large incalculable amount of the solution was either forcibly expelled from the nose or drawn into the nasopharynx and expectorated by the patient, so that only a small amount of the solution used actually remained in contact with the nasal mucosa.

At 10:35 A.M., about five minutes after completion of the anesthetization, the patient complained of sudden nausea which lasted for about two minutes. At this time it was noted that he was becoming restless and incoherent in speech, the eyes showed a "far-away" distant stare, and facial grimacing occurred. The head of the table was lowered, and by the time the patient was in a recumbent position there was intense tonic spasm of the arms and legs followed by extreme rigidity with the entire body in the opisthotonos position. Apnea and unconsciousness were immediate. Artificial respiration and oxygen by face mask were administered. The tonic spasm ceased shortly and was followed by short convulsive clonic spasms of the arms and legs and

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rapid shallow respirations. Also noted was a dead white pallor of the lower extremities. The dorsalis pedis pulsations were not obtained; the posterior tibial pulsations were moderate and of equal intensity.

Approximately ten minutes after the onset of the initial reaction, 7½ grains of sodium amytal were administered intravenously and complete subsidence of the convulsive movements occurred. At this time examination of the heart revealed a mid-diastolic gallop rhythm that was regular and at a rate of 150 per minute. The blood pressure was 140/50-0. Subsequently, the heart showed a varying arrhythmia with multiple premature contractions with compensatory pauses and runs of ectopic beats. At times there was a return to a regular rhythm at a rate of 165 per minute, the gallop persisting. At 11:00 A.M., the blood pressure was 100/50. At this time the first electrocardiogram was taken (Fig. 1).

At 11:10 A.M., the face mask was removed and an intranasal catheter was inserted. Oxygen was administered at a rate of five liters per minute for the duration of the patient's illness. A pharyngeal airway was inserted after respiratory difficulty was experienced due to relaxation of the tongue. He remained unconscious and exhibited no further convulsive phenomena until 11:45 A.M., at which time slight clonic spasms of the arms, legs, and head occurred. These were

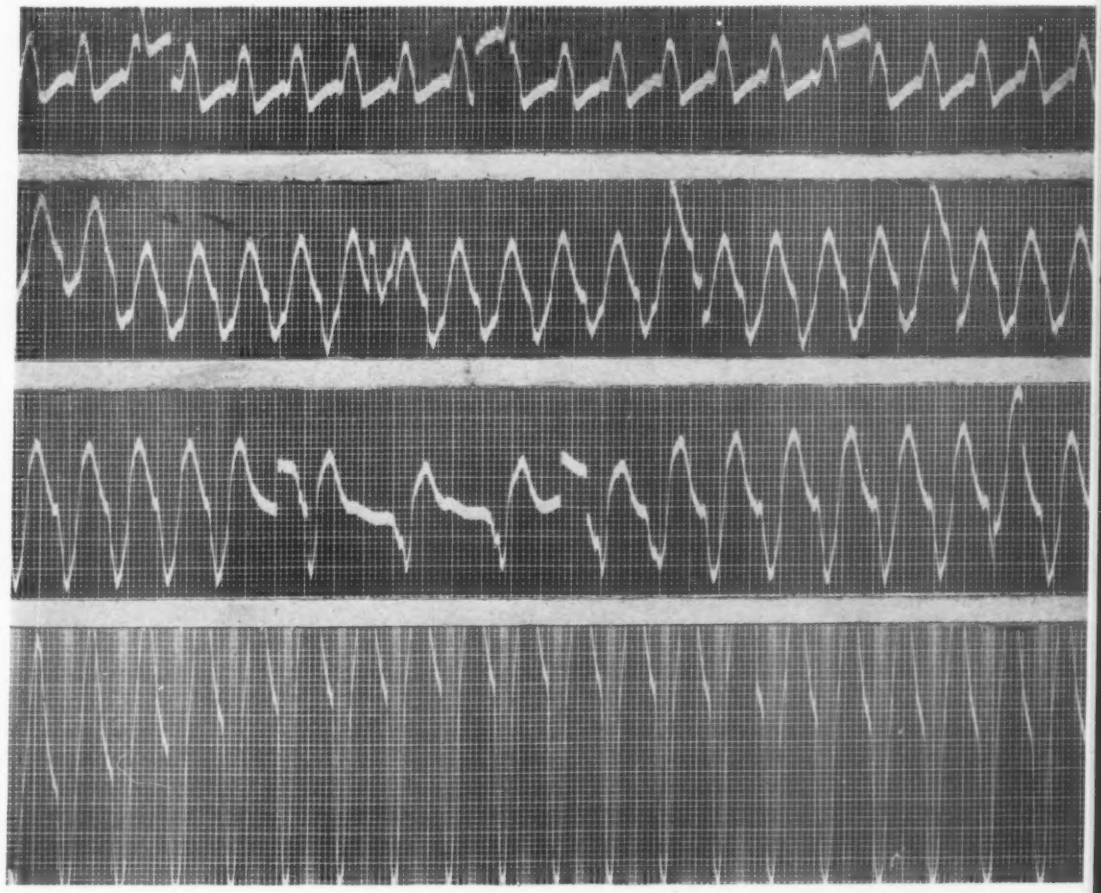

Fig. 1.—Initial tracing twenty-five minutes after onset of cocaine reaction. Ventricular tachycardia at a rate of 167 per minute is present. In Lead III there are three sinus beats with a P-R interval of 0.32 second. Ventricular conduction in these sinus beats is also aberrant.

immediately controlled by administration of 3¾ grains of sodium amytal intravenously. At this time it was noted that the pupils, which had previously been small due to the preoperative morphine, slowly and irregularly dilated. The corneal reflexes remained absent. The intense pallor of the lower extremities gradually diminished, although the dorsalis pedis pulsations did not become obtainable until approximately three and one-half hours after the initial event. An absence of sweating over the entire body during the early acute phase was also observed. This was accompanied by an axillary temperature of 101.2° Fahrenheit.

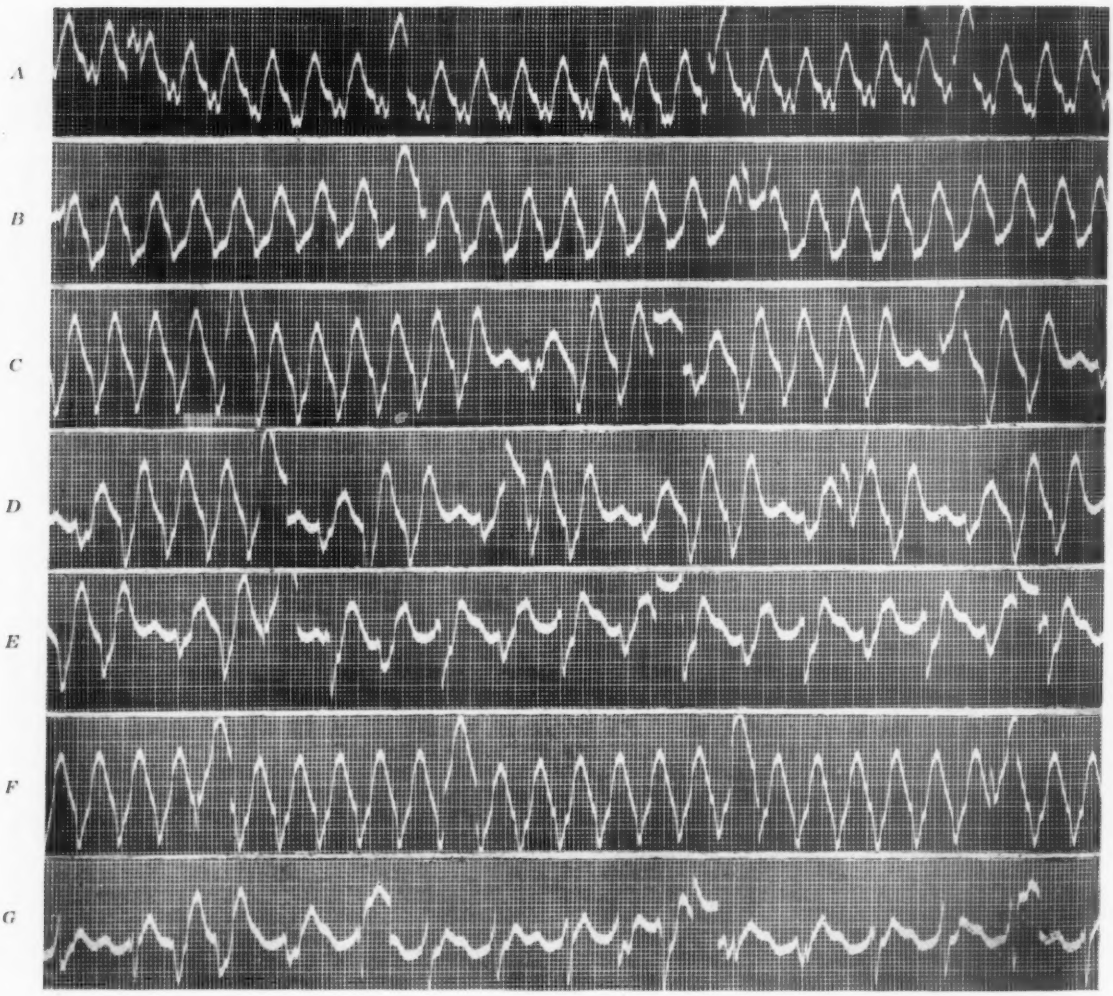

Fig. 2.—Continuous Lead II. In *A* and *B* ventricular trachycardia at a rate of 167 per minute is still present; *C* shows initial quinine effect. In *C* and *D* a basic sinus rhythm at a rate of 42 per minute has been established; runs of ventricular trachycardia occur between the sinus beats; the P-R interval measures 0.28 second. In *E* partial A-V dissociation has occurred; the auricular rate is 110 per minute; alternate auricular beats are conducted with a P-R interval of 0.24 second, giving a basic rate of 55 per minute. A parasystolic rhythm is present also at a rate of 55 per mniute. In *F* the ventricular tachycardia at a rate of 167 per minute is re-established. In *G* a regular sinus rhythm at a rate of 100 per minute is present; the P-R interval measures 0.30 second; the form of the ventricular response varies.

Because of the persistence of ventricular tachycardia, at 11:52 A.M. intravenous quinine dihydrochloride (one gram per 100 c.c. of distilled water) was started and a continuous intravenous drip of this solution was maintained to a total of six grams up to 2:00 P.M. During this period the apical rate became slower and irregular. At times runs of tachycardia were observed, but more often multiple ectopic beats, frequently resulting in a bigeminal and trigeminal rhythm, were present (Figs. 2 and 3). The blood pressure varied from 106/60 to 130/70.

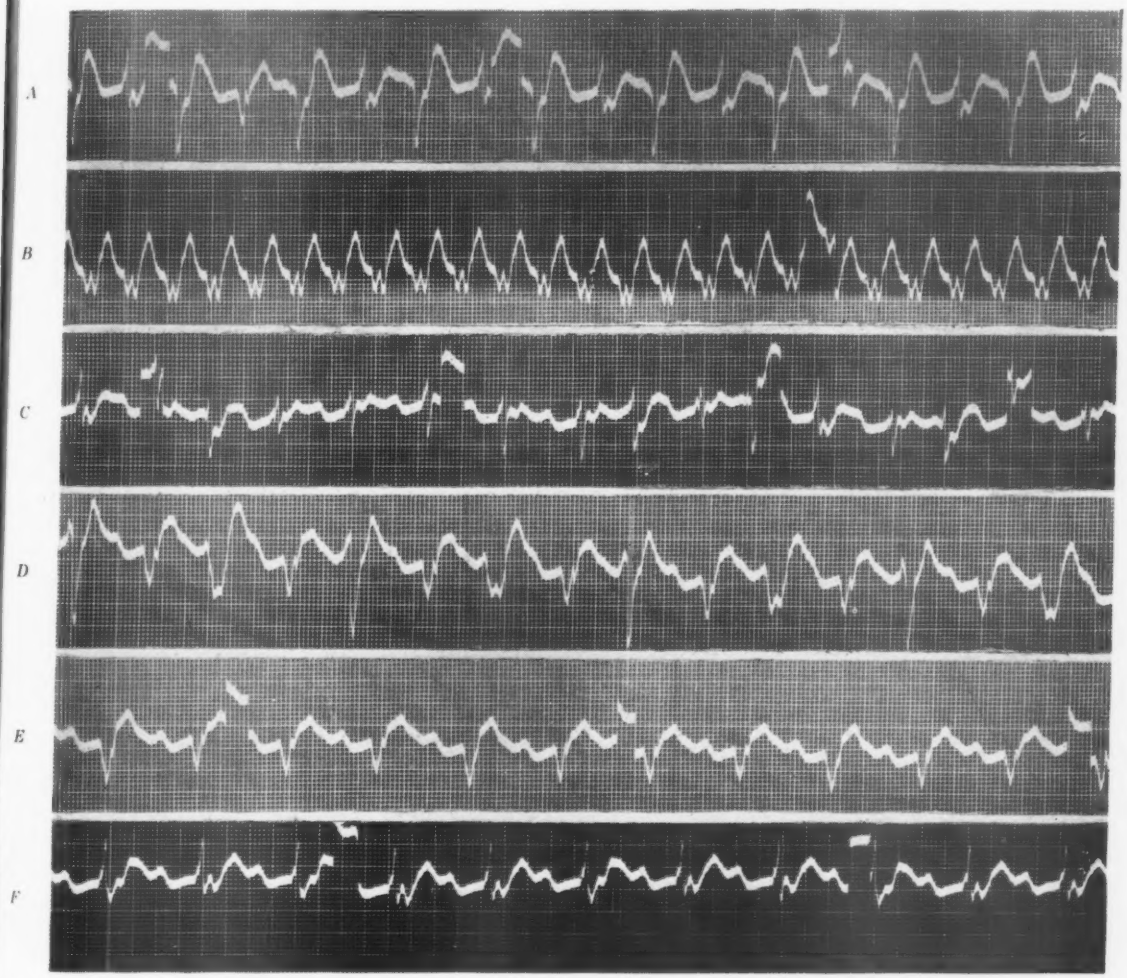

Fig. 3.—Continuous Lead II. In *A* there is total A-V dissociation with a bidirectional ventricular tachycardia at a rate of 115 per minute. In *B* the previous type of ventricular tachycardia is again present. In *C* a partial A-V dissociation with ectopic ventricular beats has occurred; the auricular rate is 167 per minute. In *D* the auricular rate is 100 per minute; alternate auricular beats are conducted with a P-R interval of 0.28 second and give a basic sinus rhythm of 50 per minute. Alternating between each of these sinus beats are two different ectopic ventricular foci, resulting in two parasystolic rhythms each at a rate of 25 per minute. In *E* a regular sinus rhythm at a rate of 75 is present; the P-R interval is 0.34 second; the QRS conplex measures 0.12 second. In *F* a 2:1 A-V block is present; the auricular rate is 150 per minute, the ventricular rate, 75 per minute.

At 2:00 P.M. the patient reacted to the extent of expelling the pharyngeal airway and coughing out a small bloody mucous plug. This was not accompanied by consciousness nor by convulsive manifestations. Shortly thereafter, for the first time since the onset of the acute episode, the apical rhythm became regular at a rate of 75 per minute (Fig. 3,*E*). The quinine dihydrochloride was then discontinued. Ten to fifteen minutes later the regular rhythm and slow rate were no longer present. Multiple ectopic beats were again observed and because of this the quinine dihydrochloride intravenous drip was again started. During the subsequent two hours another two and one-half grams of the drug were given.

Never again was there a restoration of the sinus rhythm, although the heart rate was slower than previously and the gallop rhythm was no longer noted (Figs. 4 and 5). The patient remained comatose. The axillary temperature was 101° Fahrenheit. Mild diaphoresis occurred, notably over the face and neck. There was never any clinical evidence of congestive heart failure. Suddenly at 4:02 P.M., a short convulsive seizure occurred, during which the patient's head became extended and breathing ceased although the heart continued to beat. Artifical respiration and the usual heroic measures were of no avail and the patient was pronounced dead at 4:07 P.M., five and one-half hours after the onset of the initial cocaine reaction.

At *post-mortem examination* the only abnormal findings were moderate passive congestion of the left lower lobe of the lung, the liver, and the spleen.

DISCUSSION

Circulatory changes due to cocaine intoxication may result either from an overdosage of the drug or from individual susceptibility. Small doses may decrease the heart rate by central vagal action while moderate doses result in an acceleration of the rate due to sympathetic stimulation. Large doses intravenously may cause immediate death from cardiac failure due to direct toxic action on the heart.[5] Reactions due to hypersensitivity, however, whatever may be the underlying mechanism, are completely independent of the dosage, and death has been reported from as little as 20 mg. of the drug.[5]

That the reaction in this patient was due to the cocaine seems quite certain because of the classical picture of acute cocaine poisoning presented. It is exceedingly unlikely that the small amount of epinephrine in the solution was responsible, for even if absorption of the entire 6.0 c.c. of solution sprayed had occurred, only 2 minims of epinephrine would have been absorbed with it. Because of the undoubtedly small amount of cocaine absorbed it is reasonable to assume that the reaction occurred because of an unusual degree of hypersensitivity to the drug. The circulatory effects are believed to have been of reflex central and peripheral origin, and were of two types:

1. *Vasoconstrictor*, manifested by the intense pallor of the lower extremities, absent dorsalis pedis pulsations, anhidrosis, hyperpyrexia, and transient mild rise in systolic blood pressure.
2. *Cardio-accelerator*, due to reflex central and peripheral sympathetic stimulation and manifested by the demonstrated electrocardiographic changes (Figs. 1-5).

The initial electrocardiogram was taken twenty-five minutes after the onset of the cocaine reaction, and frequent repeated tracings were recorded thereafter for the subsequent five hours. A ventricular tachycardia was present on

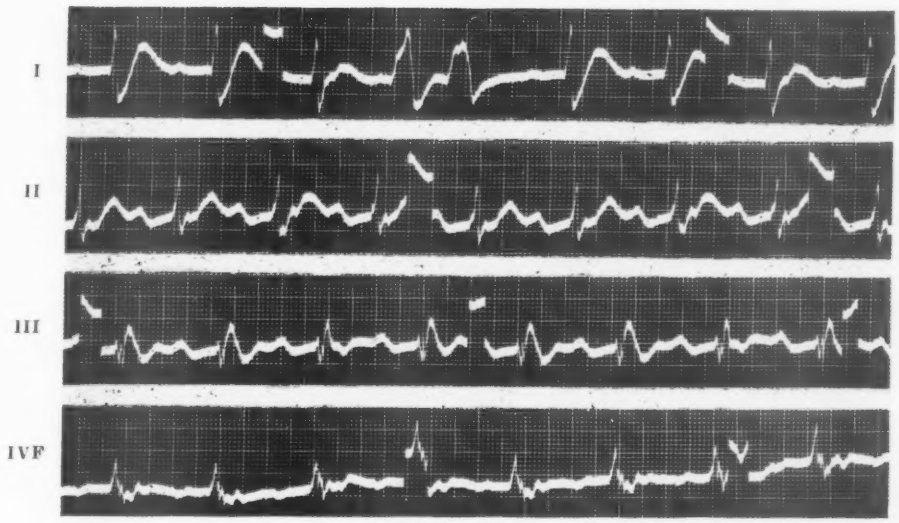

Fig. 4.—Period of 2:1 A-V heart block. The auricular rate is 142 per minute, the ventricular rate, 71 per minute. Two ectopic beats are present in Lead I. The P-R interval measures 0.38 second, the QRS complex, 0.12 second.

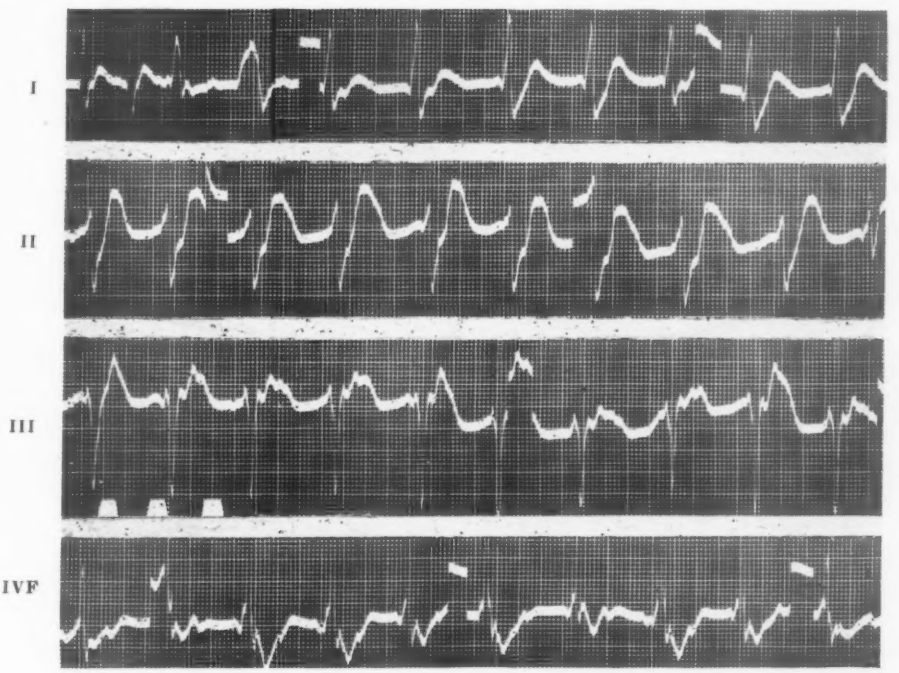

Fig. 5.—Final record. Total A-V dissociation. The auricular rate is 167 per minute, the ventricular rate, 75 per minute.

the first tracing (Fig. 1). It is important to note that the tachycardia was interrupted by a few beats of regular sinus rhythm in which both auriculoventricular and intraventricular conduction disturbances were present (Fig. 1, Lead III). This may be of significance in evaluating the later patterns of heart block and auriculoventricular dissociation because, although it is most likely that they were due to quinine, the possibility that these changes, too, may have resulted from the cocaine intoxication cannot be entirely discarded.

Except for a varying QRS pattern (Figs. 2,*A* and 2,*B*), the ventricular tachycardia persisted for one to one and one-half hours until the administration of the intravenous quinine. Although the quinine then periodically allowed a sinus mechanism to establish itself, this was accomplished only with considerable difficulty. In the early stages the ectopic ventricular pacemaker continually interrupted the attempt to maintain a sinus rhythm. Short runs of ventricular tachycardia between sinus beats, frequently resulting in trigenimal rhythm, occurred (Figs. 2,*B* and 2,*C*). Periodically, the tracing showed a complete return to the former continuous ventricular tachycardia (Figs. 2,*F* and 3,*B*). At times a partial auriculoventricular dissociation with auricular tachycardia and parasystolic rhythm appeared (Figs. 2,*E* and 3,*D*). A phase in which a bidirectional ventricular tachycardia existed was also noted (Fig. 3,*A*). At a later stage 2:1 A-V heart block was manifested for a prolonged period (Figs. 3,*F* and 4). Finally the total auriculoventricular dissociation became permanently established (Fig. 5) and remained unchanged thereafter.

The ventricular complexes were always abnormal, even when they occurred as a response to a supraventricular stimulus (Figs. 3,*D* and 3,*E*). This is undoubtedly the result of the cocaine reaction. As more quinine was administered the P-R interval became progressively prolonged, probably due to the retarding effect of quinine on auriculoventricular conduction. The varying degrees of auriculoventricular block most likely resulted from the same cause. It is possible, however, in view of the occurrence of an auriculoventricular conduction disturbance prior to quinine therapy, that these changes, too, may have resulted from the cocaine reaction or at least the cocaine may have potentiated the quinine effect.

It is interesting to note that previous descriptions of clinical cardiovascular effects of cocaine or novocaine simply mention "slowing of the heart rate,"[5,6] "tachycardia,"[5,6] or "sudden stoppage of the heart."[7] As no previous electrocardiographic studies of such reactions have been made, accurate description of the types of arrhythmia is lacking. It is possible, in view of the electrocardiographic phenomena demonstrated in this patient, that similar arrhythmias have resulted from cocaine poisoning but have not been described in other than general terms because of lack of graphic representation.

The autopsy did not reveal any abnormal findings other than moderate passive congestion of the viscera. This has been reported as common to all cases of death following the use of local anesthetics.[8] The absence of demonstrable underlying heart disease is further evidence of a primary idiosyncratic drug reaction.

Objection might be raised that the electrocardiographic changes are not comparable with those that have been obtained with the cocaine group of drugs in experimental animals. Mautz[3] has demonstrated that local application of these drugs to the dog's heart results in a monophasic type of action current of short duration and a decrease in surface irritability of the heart. Burstein and Marangoni[4] have also demonstrated reduction of myocardial irritability by the surface application of procaine. Watanabe[1] applied cocaine and novocaine to the sinus node of the frog's heart and obtained auriculoventricular dissociation. This was duplicated in the dog's heart by Shookhoff,[2] who also demonstrated right bundle branch block on injection of these drugs into the jugular vein of the dog and left bundle branch block when these solutions were introduced into a pulmonary vein. These methods, however, result in a direct toxic effect upon the myocardium and intrinsic conduction system and, as such, are not comparable to the effect demonstrated here which resulted from a primary central nervous system reaction with secondary reflex sympathetic cardiac stimulation.

SUMMARY AND CONCLUSIONS

A fatal case of acute idiosyncratic intoxication due to cocaine is described. Continuous electrocardiograms were obtained over a five-hour period. Ventricular tachycardia was the initial change recorded and, thereafter, auricular tachycardia, multifocal ectopic ventricular beats, bidirectional ventricular tachycardia, and auriculoventricular conduction disturbances occurred. All except the auriculoventricular conduction disturbances can be attributed to the cocaine reaction. It is probable that quinine therapy was responsible for the latter abnormalities, but the cocaine reaction cannot be entirely excluded as a responsible mechanism. The electrocardiographic changes due to cocaine are atrributed to reflex central and peripheral sympathetic stimulation of the heart.

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TUBERCULOMA OF THE MYOCARDIUM

A Case Report

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REVIEW of the literature indicates that cases of tuberculoma of the heart occur so infrequently as to warrant report of a single case. In the American literature, the latest report of true tuberculoma of the myocardium was that of Banyai and Van Hecke[1] in 1937. Cases of tuberculosis of the heart other than tuberculoma include Saffie's[2] report of a case of caseous tuberculosis in 1945 and Horn and Saphir's[3] report of three cases of miliary tuberculosis of the myocardium in 1935, the latter having comprehensively reviewed the literature as of that date.

In the more recent foreign literature, Bose[4] has reported a case of tuberculosis of the heart which he states, "to the naked eye, appeared as a neoplasm." In 1936, Masugi and co-workers[5] reported the occurrence of granulomas resembling Aschoff bodies in the heart of a patient with pulmonary tuberculosis; and in 1937 Pfeil[6] mentioned thirty-one cases of tuberculous involvement of the myocardium in 2,074 patients who died of tuberculosis. The following case is a rather classical one of tuberculoma of the myocardium, both from the clinical and pathologic point of view.

CASE REPORT

R. D., a 20-year-old colored World War II veteran, was admitted to this hospital on June 3, 1944, with the following history: Physical examination, including chest x-ray, showed essentially normal findings on induction into the service in March, 1943. About September, 1943, he began to complain of left pleuritic pain. Because of an elevated temperature he was admitted to the station hospital where examination revealed a left pleural effusion. Repeated aspirations of the left chest were negative for organisms until November, 1943, when tubercle bacilli were found. At this time the sputum was negative.

His chief complaints on admission to this hospital were pain in the left chest, weakness, loss of weight, and dyspnea. Physical examination revealed nothing remarkable. His weight was 144 pounds; height, 71¾ inches; blood pressure, 110/84; pulse rate, 96 per minute; and temperature, 98.6° Fahrenheit. There was restricted mobility of the left chest with diminished tactile fremitus, dullness to flatness on percussion, and absent breath sounds. Laboratory findings revealed tubercle bacilli in sputum and chest fluid.

In July, 1944, tuberculous involvement was discovered in the right lung and a right phreniclasia was performed. At this time he began to experience abdominal distress manifested by gastric distention, diarrhea, and occasional bloody stools. Concomitantly, he developed cold abscesses of the back and of the anterior surface of the left chest. Smears from the abscesses were positive for acid-fast bacilli. At no time were there any complaints referable to the cardiovascular system and no electrocardiogram was made. Barium meal in February, 1945, was negative for any pathology. X-ray films of the spine and ribs were negative for caseous tuberculosis. Wasser-

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mann and Kline tests were negative. Blood count, urinalysis, and blood chemistry were all within normal limits. The erythrocyte sedimentation rate was 22 mm. in one hour. Repeated chest films revealed a small amount of fibrosis in the area of the first and second right intercostal space. The remainder of this lung showed no evidence of disease. The left lung was considerably compressed by fluid at the base. He gradually became cachectic and finally expired on Dec. 5, 1945. Clinical diagnoses were: Chronic moderately advanced pulmonary tuberculosis with serofibrinous involvement of the left pleura and multiple cold abscesses.

Autopsy Findings.—The body was that of a tall, undernourished colored man, 22 years of age. There was a sinus tract opening on the left posterior chest wall in the midscapular line about the level of the eighth rib. There was softening of the manubrium.

Fig. 1.—Circumscribed tuberculoma in the wall of the left auricle, showing close relationship to the base of the mitral valve.

The heart weighed 250 grams. There were three yellowish-gray nodules present; one located at the base of the mitral valve, 2 cm. in diameter (Fig. 1), and two others located in the myocardium of the left atrium which were somewhat smaller (Fig. 2). Heart valves were normal. The coronary vessels were patent and there was no thickening of their walls. The aorta was smooth.

There was a left empyema containing 400 c.c. of purulent fluid. Both lungs were adherent. The left lung was collapsed and weighed 500 grams. A few small tubercles were noted in the left apex. The pleura was thickened. The right lung weighed 300 grams. It was normal grayish pink on section, except for numerous shotlike tubercles scattered throughout the apex.

The spleen weighed 100 grams. Surface was normal and the cut section revealed a few small pinhead-sized tubercles. The parenchyma was smooth and dark red in color. The liver weighed 1,350 grams. The surface was smooth except for three or four fairly large tubercles averaging

0.5 cm. in diameter. Cut section revealed a mottled grayish-brown color. It was soft and friable. The gall bladder was normal.

The esophagus and stomach were grossly normal. There were numerous fairly large tuberculous ulcers present in the terminal ileum and in the cecum. The serosa of the entire bowel was studded with tubercles. The mesenteric nodes were large and caseous, most of them being the size of walnuts. The pancreas was normal.

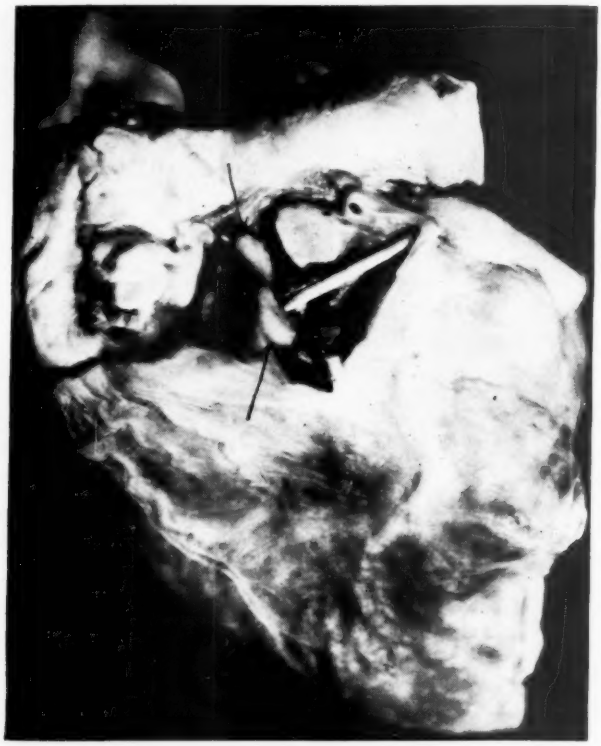

Fig. 2.—Two small tuberculous nodules in the wall of the left auricle as seen after the splitting of the epicardium and sectioning.

Combined weight of the kidneys was 280 grams; a few fairly large light yellow tubercles were seen on the surfaces. Both adrenals showed almost complete replacement by large areas of caseation, so that almost none of the cortex remained intact. They were approximately four times normal size.

There was a large cold abscess surrounding the bodies of the entire thoracic spine which communicated with the sinus opening mentioned above. Within the abscess cavity, small particles of bone were noted floating free in the purulent material. The spine was sectioned longitudinally and the bodies of all the vertebrae showed caseous necrosis which was most extensive in the tenth, eleventh, and twelfth thoracic segments.

Histology: There were many typical tubercles and a few small areas of caseation in sections from the lungs. In sections from the heart, there were two large areas of caseation imbedded in the myocardium and completely surrounded by muscle cells. The caseated areas were within a zone of epitheliod cells in which a few giant cells of the Langhans' type were noted. In sections from the kidneys there were many hyaline casts in the tubules. There were areas of caseation necrosis and a few typical tubercles. In liver sections there were scattered tubercles; the sinuses

were filled with red cells and serum. There was massive replacement of the entire medulla and most of the cortex of the adrenals by areas of caseation. Many typical tubercles were seen in sections from the spleen.

DISCUSSION

Myocardial tuberculosis occurs in three main forms: (1) miliary, (2) nodular, and (3) infiltrating. Of these, the nodular variety as encountered in this case, is, relatively, the most frequent. This form usually occurs as yellowish-gray, rounded, fairly firm nodules which may vary in size from less than a centimeter to the size of an egg. They may be well defined or merged with the surrounding parenchyma. The common site is the wall of the right auricle. Their ability to produce symptoms, of course, depends upon their size and location. Most of the reported cases have been without subjective or objective signs of cardiac involvement, with a few notable exceptions. In Adamson's[7] case, "the auricles were so markedly involved with multiple variously-sized masses, that it seemed they couldn't contract." The cases of Maurocordat[8,a] and Townsend[8] showed nodules of the auricles so large that the bloodflow in the pulmonary veins was obstructed, with resulting hemorrhage into the lungs and death from asphyxia. Binder[9] reported a case in which there was obstruction to the auricular blood flow by a large tuberculoma of the left auricle. In Eisenmenger's[10] case, a large tubercle about the size of a lemon in the wall of the right auricle caused compression of the auricular lumen. Banyai and Van Hecke's[1] report was similar to our case in that there was no clinical evidence referable to the heart.

SUMMARY

A case of nodular tuberculosis (tuberculoma) of the heart is presented, together with a summary of the recent literature. Although there were three nodules in the left auricle, one of which involved the base of the mitral valve, yet at no time was there any clinical evidence referable to the cardiovascular system.

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DAILY CHANGING PICTURE IN A CASE OF ACUTE RHEUMATIC CARDITIS

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IT IS well known that cases of acute rheumatic carditis show frequently changing pictures, but few examples have been found in the literature exhibiting marked daily electrocardiographic changes, probably because such serial tracings are not ordinarily taken. Pease, Steuer, and Peters[1] have called attention to the value of routine serial electrocardiograms in acute rheumatic fever; in bringing to light evidence of myocardial damage which otherwise might escape detection. They state that single electrocardiograms might prove confusing because of the presence of T waves very like "coronary T" waves. Myocardial involvement and pericarditis may remain unsuspected without serial electrocardiograms. They report three cases showing electrocardiographic evidence of cardiac damage which otherwise might have remained undetected. Pardee[2] has pointed out the large number (more than 60%) of cases of acute rheumatic carditis which show persistent T-wave changes suggestive of myocardial disease. Barnes[3] has summarized the evidence on electrocardiographic changes in pericarditis, which points to the conclusion that the RS-T segment and T-wave changes in pericarditis, in most instances at least, are due to an inflammatory reaction in the subepicardial myocardium. Barnes also states that serial tracings, taken over a period of days or even weeks, may be necessary to distinguish the tracings of pericarditis from those of acute myocardial infarction.

A case of acute rheumatic carditis is reported in which daily electrocardiograms were taken over a twelve-day period, and after that time less often but still frequently, to demonstrate the daily reversible and recurring changes in RS-T segments, T waves, and QRS complexes. It is shown graphically by the electrocardiograms themselves how a single tracing could be confusing.

CASE REPORT

C. W., a 32-year-old white man, was admitted to the hospital where these studies were made on March 24, 1945. Family history and past history were essentially negative except for frequent colds and sore throats. Two weeks before admission he developed a cold and sore throat. Six days later he developed malaise, fever (101 to 102° F., oral), slight cough, chest pain, moderate sweating, and chilly sensations. He was given sulfatherapy at home for five or six days, without benefit, for "pneumonia." Upon admission he seemed toxic, and appeared acutely ill. Physical

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examination revealed frank signs of a right lower lobe pneumonia (dullness to percussion, diminished breath sounds, increased voice sounds, increased tactile fremitus, and a few fine râles), with oral temperature of 102° F. No evidence of cardiac involvement was found. He received penicillin intramuscularly, 40,000 units every three hours for the first twenty-four hours after admission, without effect. He remained toxic, and x-ray films of the chest taken upon admission showed a clear right base with "thickened pleura" at the left base. On March 25, the day after admission, a to-and-fro moderately harsh friction rub was present over the cardiac apex and lower sternum. An electrocardiogram showed an elevation of the RS-T segment in Leads I and II, and a P-R interval of 0.26 second with a heart rate of over 100 per minute. That night, March 25, he developed pain, swelling, heat of both knees with voluntary muscular rigidity, and pain of the right elbow. Turbid fluid from the left knee gave a white blood cell count of 6,300 per cubic millimeter, with 88 per cent neutrophiles. He was put on intensive salicylate therapy by mouth, with almost immediate marked improvement. On March 27, the temperature was 98° F., he was not toxic, felt well, the pulse rate was 84 per minute, and the lung fields were not abnormal to physical examination; he moved his elbow and knees freely, the knee joints showed no fluid clinically. From then until discharge, the patient felt well. However, he showed frequent changes in physical examination of the heart, in x-ray examination of the heart, and in serial electrocardiograms.

Frequent blood examinations between March 24 (the day of admission) and July 2 (nine days before discharge) revealed white blood cell counts ranging from 5,700 to 13,800 per cubic millimeter, with from 45 to 87 per cent neutrophiles. Frequent sedimentation rates (corrected

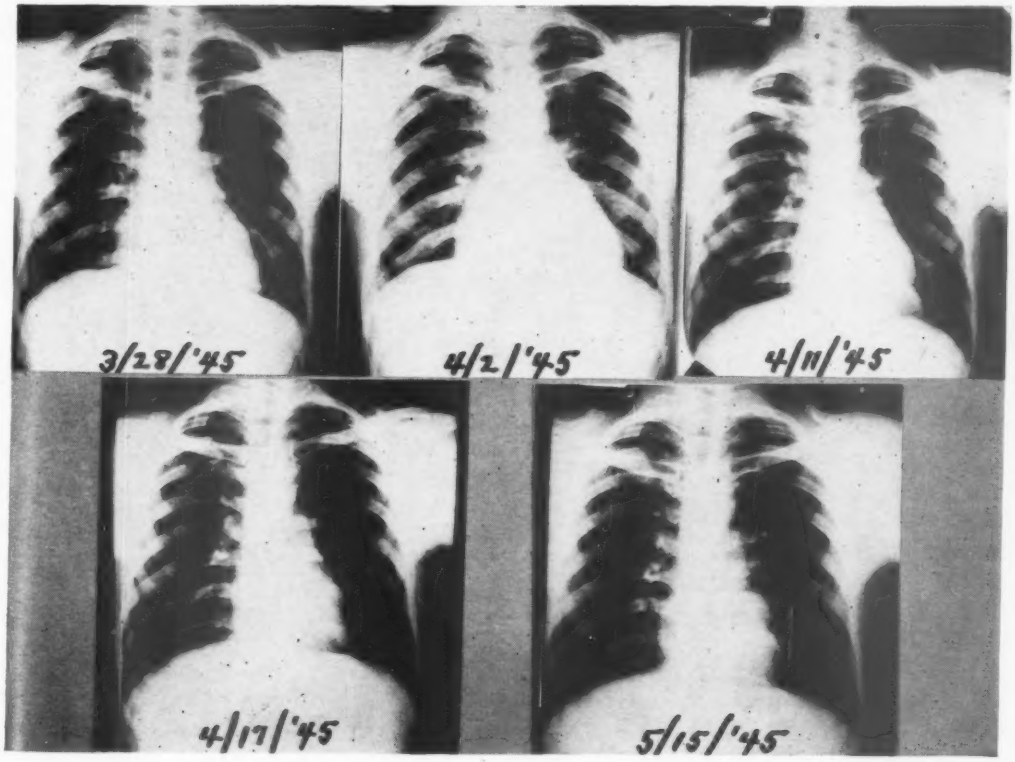

Fig. 1.—Teleroentgenograms (6-foot) x-rays taken during the course of the disease.

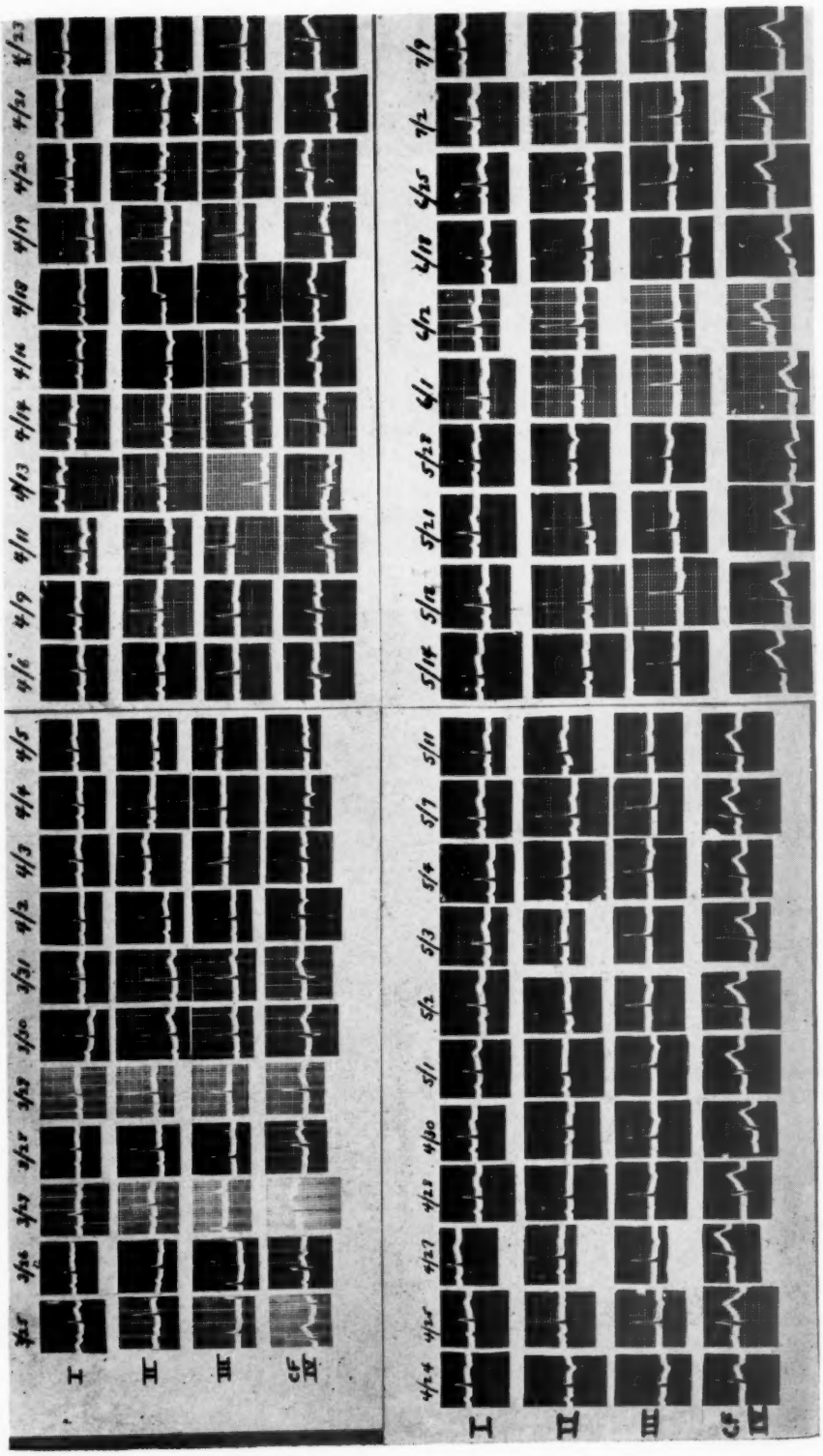

Fig. 2.—Serial electrocardiograms taken during the course of the disease.

for hematocrit) between March 26 and May 31 ranged from 18 to 43 mm. per hour (all but one determination being above 25 millimeters). From May 31 to July 2 there was a gradual decrease in the sedimentation rate to 4 mm. per hour.

COMMENT

Physical Examination of the Heart.—The pericardial friction rub changed frequently (often daily) in intensity and quality until it disappeared on April 10. On March 28, for the first time, a very soft apical systolic murmur was heard. The murmur changed often, and at times, daily in intensity, quality, and point of maximum intensity (apex and third left interspace next to the sternum) until May 14. From then until discharge a soft apical systolic murmur was heard.

X-ray Examination of the Heart.—Numerous teleroentgenograms were taken. During the course of the acute stage of the disease these showed an increase, and then a decrease to normal, of the cardiac shadow. These changes are illustrated in Fig. 1.

Electrocardiograms.—Serial electrocardiograms were taken, at first daily, then several times per week, and finally about once a week. At first, these tracings showed a constantly changing picture. Later, changes continued to appear, but less frequently. Involved in the changes were the P-R interval (generally prolonged), the T waves, the RS-T segments, the QRS complexes in Lead IV F, the heart rate, the amplitude of the QRS complexes in all leads, and the presence or absence of phasic sinus arrhythmia. The last few tracings showed stabilization with no change. They were essentially normal except for a low T wave in Lead II. The changing electrocardiographic picture is illustrated in Fig. 2.

Therapy.—Intensive salicylate therapy was continued from March 26 to April 23, and again from May 22 to May 31. Blood salicylate levels ranged from 6.9 to 62.8 mgm. per cent.

SUMMARY

A case of acute rheumatic carditis is reported to show the daily electrocardiographic changes during the acute phase of the disease. These changes occurred in the RS-T segments, T waves, and QRS complexes primarily, and were from day to day reversible and recurring. This changing picture indicates the interest and importance attached to the taking of serial tracings in cases of acute rheumatic carditis, for one tracing may be confusing diagnostically.

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ASYMPTOMATIC CONGENITAL ANOMALY OF THE HEART: CONGENITAL MUSCULAR CORD BRIDGING WALLS OF AURICLE ABOVE CENTER OF MITRAL VALVE

LIEUTENANT COLONEL W. L. MCNAMARA AND LIEUTENANT COLONEL L. A. BAKER, MEDICAL CORPS, ARMY OF THE UNITED STATES, AND KENNETH COSTICH, M.D., HINES, ILL.

WE CAN find in the literature no description of a case presenting anomaly of the heart similar to the variation which forms the basis of this report. This anomaly, a muscular cord bridging the walls of the left auricle above the mitral valve, did not in any way disturb the function of the heart and was never the cause of clinical symptoms. It was discovered during routine examination of the heart at autopsy of a patient in whom death had been caused by cancer of the esophagus.

REPORT OF CASE

The patient was a Negro man, 54 years of age, who entered the hospital in the terminal stage of carcinoma of the esophagus. The Wassermann was negative. There was no history of syphilis or of heart disease.

Autopsy.—There was a carcinoma of the esophagus at the junction of the middle and upper thirds. It had caused obstruction and perforation with resulting suppurative mediastinitis. Metastases were demonstrated in the regional lymph nodes and mediastinum.

The combined weight of the kidneys was 400 grams. Both kidneys showed the same gross appearance. The capsules stripped with difficulty, but the surface was fairly smooth except for multiple cysts, the largest of which measured 8 mm.; the smallest was the size of a pinhead. These cysts were scattered throughout the cortex of the kidney and were noted in the parenchyma on section. The cysts contained clear fluid and were lined with a grayish glistening membrane. There was no evidence of arteriosclerosis or scarring. A diagnosis of multiple congenital cysts of the kidney was made. The bladder, prostate, vesicles, and testes showed no evidence of pathologic changes.

The aortic arch was smooth and there was practically no arteriosclerosis throughout the entire length of the aorta. The peripheral blood vessels were essentially normal.

The heart weighed 400 grams. There was a small amount of fibrous pericarditis. The muscle was somewhat softer than normal. There was no evidence of hypertrophy or dilatation. The coronary arteries were smooth. On section of the heart an anomaly was noted in the left auricle; a smooth round cord extended from one side of the wall immediately above the base of the mitral valve across the cavity to the other side in the same region. The cord was smoothly covered with endocardium continuous with that of the auricular walls. The two points of attachment to the walls were cone-shaped. The length of the cord arising from the apices and of the cones measured 3.5 centimeters.

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The base of the cone-shaped attachment measured 3.5 mm. in diameter, and the diameter of the remainder of the length of the cord was 2 millimeters.

The valve leaflets were normal and showed no evidence of insufficiency to the water test.

There was no evidence of an inflammatory process either in the endocardium of the auricle or the endocardium covering the valve. The mitral valve measured 4 cm. across, parallel to the valve opening. The papillary muscles were normal. The aortic valve was normal in appearance, and the tricuspid and pulmonary valves presented no signs of abnormality. There was no endocardial thickening. No evidence of hypertrophy was noted.

Histologic examination of a section of the cord showed it to be composed of cardiac muscle, smoothly covered by endocardium. (Fig. 1.)

Fig. 1.—Opened left auricle showing muscular band bridging walls.

DISCUSSION

The structure of this cord would suggest conclusively that it was a congenital anomaly. No explanation is offered of its origin from the standpoint of embryology.

Stohr[2] in a study of malformations of the heart in the newborn concludes that the present view tends to assign the majority, if not all, of the congenital defects to abnormalities of development. However, she reports two cases of abnormal hearts in newborn infants in which, she felt, detailed histologic examinations tended to prove the inflammatory nature of the lesions.

In the case described in this paper, the structure was composed of an orderly arrangement of cardiac muscle covered by a smooth reflection of the endocardium of the auricle walls. There is nothing to suggest remotely an inflammatory process as an etiological factor.

Of special interest in this case is the occurrence of multiple congenital cysts of the kidney. In cases of congenital cardiac anomalies concomitant anomalies

in other organs of the body have frequently been noted. Thus, Vierordt (quoted by Stohr[2]) estimated that other anomalies such as harelip, syndactylism, horseshoe kidney, and hypostadius are found in about 10 per cent of the cases of congenital heart disease.

Rannels and Propst[1] in a study of autopsy records at the Hospital of the University of Pennsylvania found thirty-six cases of cardiac congenital anomalies. In five of these cases there were associated congenital deformities.

SUMMARY

A congenital anomaly of the left auricle is described. There was a concomitant congenital defect of the kidneys. This cardiac anomaly produced no symptoms, and was accidently discovered at autopsy on a patient who had died of carcinoma. A search of the literature has failed to show the report of a similar anomaly.

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ERRATA

In the March, 1947, issue of the AMERICAN HEART JOURNAL, in the abstract entitled "The Effect of Age on the Clinical Effectiveness of Nitroglycerin Tablets," on page 401, the senior author's name was misspelled. It should be Sagall rather than Segall.

The following two errors appeared in the June, 1947, issue of the JOURNAL:

In the paper entitled "Significance of Abnormally Small QRS Deflections in One or More Precordial Leads" by Albert W. Lapin, M.D., on pages 754-756, in Table IV, under the columns headed Pleural or Pericardial Effusion or Ascites, Congestion or Edema of the Lungs, and Peripheral Edema, the dashes should be plus signs.

The ninth line of the third paragraph on page 760 should read "In this case Leads V_5 and V_6," etc. instead of "In this case Leads V_4 and V_6," etc.

Abstracts and Reviews

Selected Abstracts

Dack, S., and Moloshok, R.: Cardiac Manifestations of Toxic Action of Emetine Hydrochloride in Amebic Dysentery. Arch. Int. Med. **79**:228 (Feb.), 1947.

The authors report nine patients, between the ages of 18 and 37 years, with amebic dysentery, who presented toxic effects following the administration of emetine hydrochloride. These patients were given between 7 and 22 grains of the drug. All but two patients developed some dyspnea or tachycardia, three developed apical systolic murmurs, and one developed gallop rhythm. Inversion of the T wave in two or more leads was recorded in all cases, and changes in the QRS complex were reported in two cases. The authors feel that patients who are taking emetine should be followed by electrocardiograms at short regular intervals.

The time of appearance of the electrocardiographic abnormalities also varied in each case, and was often delayed until one or two weeks following the discontinuation of treatment. Owing to this lag in the appearance of electrocardiographic changes, their absence cannot be safely utilized as a criterion for the continuation of emetine hydrochloride therapy beyond a certain dose.

Electrocardiographic abnormalities, when present, were of long duration, often persisting for two months or more following cessation of treatment. This suggested prolonged fixation of the drug in the myocardium or actual myocardial degeneration as the basis for the cardiac manifestations.

Toxic effects on the neuromuscular and gastrointestinal systems generally preceded the appearance of toxic cardiac effects. The former as well as the latter are indications for the discontinuance of further therapy with emetine hydrochloride. HORWITZ.

Loewe, L., and Alture-Werber, E.: The Clinical Manifestations of Subacute Bacterial Endocarditis Caused by Streptococcus s. b. e. Am. J. Med. **1**:353 (Oct.), 1946.

In a previous paper (J. A. M. A. **130**:257, 1946) Loewe and co-workers described a new variety of a nonhemolytic streptococcus which was named *Streptococcus s.b.e.* In the present paper the authors report 115 consecutive and unselected patients with subacute bacterial endocarditis, of whom forty were infected with *Streptococcus s.b.e.* Of these forty patients, nine who were completely resistant to therapy died of the streptococcal infection, two died of congestive heart failure, and one developed a terminal *Staphylococcus aureus* infection. Four of these twelve fatalities were due to intracranial hemorrhage. Six of the remaining twenty-eight patients developed recurrence of infection, whereas there were no recurrences in the patients infected with other varieties of streptococci.

It was impossible to predict treatment success on the basis of in vitro penicillin sensitivity tests. Although the *Streptococcus s.b.e.* appeared to fall within the same range of in vitro sensitivity to penicillin as other streptococci, the total penicillin requirements and the treatment days for this organism far exceeded the quantity of pencillin and the treatment span required for infections due to *Streptococcus mitis* and *Streptococcus bovis.* Whereas these latter organisms were successfully treated by a dosage schedule of 500,000 units of penicillin daily for five weeks, the *Streptococcus s.b.e.* strain required two million units daily for eight weeks.

Whenever possible, the penicillin was given intravenously with heparin for prevention of venous thrombosis. FRIEDLAND.

Kossmann, C. E.: Relative Importance of Certain Variables in the Clinical Determination of Blood Pressure. Am. J. Med. **1**:464 (Nov.), 1946.

Four variables affect blood pressure in the arm as determined by the usual sphygmomanometric method. These are: the position of the subject (standing or recumbent), the venous content, the thickness, and the position of the arm. The position of the arm with reference to heart level is exceptionally important because of the hydrostatic pressure exerted by the column of blood between the heart level and the part of the vessel over which the Korotkoff sounds are ausculted. Thus, in 32 normal men the blood pressure in the brachial artery in the pendent arm exceeded by an average of 11.3 mm. Hg the pressure in the same arm when held at heart level.

The venous content of the arm affected blood pressure much less significantly. In the recumbent position the systolic pressure averaged 4.3 mm. Hg less "after drainage" than "before drainage" and the average diastolic pressure differences before and after drainage were negligible. In the standing position drainage did not significantly affect either systolic or diastolic pressure in the arm held at heart level. In the pendent arm the systolic pressure did not change "after drainage" but the diastolic pressure was lower by an average of 3.3 mm. of mercury.

A significant correlation was found to obtain between the circumference of the arm and the diastolic pressure. There was no correlation between this factor and the systolic pressure. The fact that the blood pressure in the two arms is different is mentioned but no data are given.

FRIEDLAND.

Webb, A. C.: Truncus Arteriosus Communis Persistens. Arch. Path. **42**:427 (Oct.), 1946.

The author reports the thirty-eighth recorded case of truncus arteriosus communis persistens. This anomaly was found in a 6-month-old white male infant who, from the time of birth, had cyanosis and dyspnea. Death was caused by acute respiratory infection terminating in bronchopneumonia.

Necropsy showed a centrally placed heart, from the base of which a single great vessel made its exit. The ostium of this common aorta (truncus) was immediately above a ventricular septal defect and approximately two-thirds over the right ventricle. There was also a patulous foramen ovale and a deformed tricuspid leaflet. The blood supply to the lungs was provided by two arterial branches of a patent ductus arteriosus. No fibrous cord indicative of pulmonary artery atresia could be found. The highly characteristic four semilunar leaflets were not present in this case, and the author emphasizes (as did Abbott) that this finding is not essential to diagnosis.

GOULEY.

Pratt-Thomas, H. R.: Tuberous Sclerosis With Congenital Tumors of Heart and Kidney. Report of a Case in a Premature Infant. Am. J. Path. **23**:189 (March) 1947.

The author presents the case of a premature Negro infant (eighth month) who died three days after delivery. It breathed spontaneously after being normally delivered, and was apparently well until the third day when cyanosis became marked and respiration difficult. The mother, 19 years old, had shown in this, her first pregnancy, leg edema, marked albuminuria, and hypertension. Serologic tests for syphilis were negative.

The child weighed 1,655 grams, was small and poorly developed. Necropsy revealed striking lesions of tuberous sclerosis in the heart and brain. A smooth round tumor projected from the apex of the heart. Very small nodules were noted in the right auricle and ventricle; all of them were pale reddish-tan, generally well demarcated. Multiple nodules were scattered throughout the brain, the most prominent being in the right frontal lobe.

Microscopic examination showed the cardiac nodules to be composed of huge cells, round or oval, the cytoplasm of which was completely clear or else finely granular. Mitosis was not seen. Striated myofibrils often radiated from central nuclei, so-called "spider cells." Cross striations were evident. Many very small nodules blending with normal myocardium were seen microscopically. Best's carmine stain revealed glycogen in the cytoplasm of some of these

cells, even in tissue preserved in formalin for eighteen months. The brain nodules showed changes including gliosis and degeneration involving both nerve and glial cells. One nodule was truly neoplastic.

Kidney section revealed focal tubular dilatations, a feature noted in many of these cases.

The author comments (as did other writers) on the close relationship between cardiac rhabdomyoma and tuberous sclerosis. Of interest is the rarity of this process in the Negro race.

GOULEY.

Saphir, Otto: Myocardial Granulomas in Subacute Bacterial Endocarditis. Arch. Path. **42**:574 (Dec.), 1946.

In a discussion of myocardial granulomas in subacute bacterial endocarditis, Saphir emphasizes the nonspecific aspects of the Bracht-Wächter lesions. He has found Aschoff bodies in 34 per cent of a group of fifty-five cases of subacute bacterial endocarditis, mostly in adolescents. In fatal cases treated with sulfa drugs and with penicillin, he has noted small foreign body granulomas surrounding a central deposit of calcium. These were scattered throughout the myocardium; they did not contain bacteria.

Saphir believes that these calcific foreign body granulomas are of embolic origin, arising from healing vegetation on the valves undergoing calcification. He saw small calcific particles in arterioles which he considered to be further evidence of their embolic origin.

A critical consideration of the literature on Bracht-Wächter bodies indicates that they signify no definite entity and that, therefore, the term "Bracht-Wächter body" should be discarded.

GOULEY.

Resano, J. H.: Dysphagia Caused by Aortic Aneurysm Treated by Ligation of the Decending Thoracic Aorta and Forward Displacement of the Esophagus by Forming a New Hiatus. Rev. clín. españ. **21**:479 (June), 1946.

A case is described in which there was present extreme dilation of the ascending and descending portion of the aorta which produced displacement and stenosis of the esophagus resulting in dysphagia. Compression of the esophagus occurred at an area of relative aortic stenosis between the dilated ascending and descending portions of the aorta. At operation a cellophane band was placed around the aorta at the site of esophageal pressure and the esophagus was separated from the aorta and moved anteriorly by forming a new hiatus in the diaphram. Following operation dysyphagia disappeared. An angiocardiogram taken one year after the operation revealed a coarctation of the aorta at the site of the ligature.

HECHT.

Alvarez Mena, S.: The Normal Esophageal Electrocardiogram. Rev. cubana de cardiol. **7**:73 (April-June), 1946.

Unipolar esophageal leads were obtained from twenty-five normal individuals. Large biphasic auricular deflections were recorded when the exploring electrode was located 30 to 35 cm. from the teeth. These records exhibited an intrinsic auricular deflection demonstrating the arrival of the action current underneath the exploring electrode. The ventricular deflections revealed small Q waves (less than 3 mm.) at ventricular levels, given as 55 cm. from the teeth. When the electrode was moved cephalad, the Q waves increased in amplitude and at auricular levels a deep QS deflection was noted in 40 percent of the cases. Maximum height of R was noted at levels 50 cm. from the teeth, S waves were inconstant, and T waves were always positive. The small Q waves observed at ventricular levels are interpreted as evidence of early activation of the right side of the interventricular septum.

HECHT.

Alzamora Castro, V.: Observations on the Significance of Changes of the ST Segment and the T Wave. Gac. méd., de Lima **9**:285-309, 1946.

In patients with evidence of coronary artery disease a standard exercise test may change the direction and shape of the T waves. A flat T wave may become upright and a diphasic or inverted T wave may change toward a more "normal" pattern. It is assumed that a "fatigue factor A,"

present in or released by the heart muscle during stress, is capable of altering the balance of electrical forces during the process of reactivation. Under these conditions an upright T wave may reflect a more abnormal myocardial state than an inverted T wave. Examples of records taken during episodes of acute anginal pain reveal a reversal of a previously inverted T without significant elevation of the S-T segment in many unipolar precordial leads. Reversal of a previously inverted T in V_R was frequently noted. HECHT.

Jimenez-Diaz, C., Arjona, E., Ales, J. M., Grande, F., Lopez Garcia, E., and Oya, J. C.: The Influence of Alterations of Bloodflow Through the Lesser Circulation Upon Volume and Elasticity of the Lungs. Rev. clín. españ. **21**:207 (May), 1946.

Perfusion experiments on isolated lungs of dogs demonstrated that overloading of the vascular system of the lungs resulted in increased aeration of the lungs similar to that seen in acute pulmonary emphysema. Under these experimental conditions the lungs appear to be more rigid and resemble the state observed in experimental asthmatic shock. It is concluded that both bronchial and "cardiac" asthma may result from acute overloading of the lesser circulation. HECHT.

Oritz de Landazuri, E., Perianes Carro, J., and Merchante Iglesias, A.: Treatment of Subacute Bacterial Endocarditis With Penicillin. Rev. clín. españ. **22**:466 (Sept.), 1946.

Fourteen patients with subacute bacterial endocarditis in the bacteremic phase were treated with sodium penicillin. Nine recovered from the acute phase of the disease and the cases may be considered to be arrested. The dosage ranged from 100,000 to 750,000 units daily with a total from 1 to 52 million units. The duration of treatment was short; the longest period covered 135 days (death), the shortest seven days (survival). Penicillin was administered without anticoagulants by intermittent intramuscular or intravenous injections and by continuous intramuscular and intravenous drip infusions. Sodium benzoate was added (10 Gm. per day) when a clinical response was not readily obtained from penicillin alone. There was no apparent correlation between the response to treatment and the number of colonies per c.c., the severity of the clinical symptoms, and the dose of penicillin. HECHT.

Mugica Echarte, J.: The Functional State of the Vascular System in Pulmonary Tuberculosis. V. The Lungs as Blood Depots. Rev. clín. españ. **21**:403 (June), 1946.

In nine patients suffering from pulmonary tuberculosis in whom a pneumothorax was induced and in one additional patient, in whom an artificial paralysis of the phrenic nerve was induced, the blood volume increased considerably after the procedure. The total circulating blood volume rose from an average of 4,600 to 6,350 ml., circulating plasma volume from 2,530 ml. to 3,400 ml., and blood volume per kilogram of body weight from 77 ml. to 104 milliliters. The volume of packed red cells did not change appreciably. It is assumed that the lungs function as blood depots and discharge their contents when collapse therapy is instituted. HECHT.

Duffau, G., and Sepulveda, M.: Rheumatic Nodules in Children. Arch. d. Hosp. niños Roberto del Río **14**:127 (Sept.), 1946.

Twenty-eight of 186 children admitted to the hospital during a six-year period with the diagnosis of acute rheumatic fever exhibited typical rheumatic nodules. They were most frequently localized at elbows and knees. All but one of the children with nodules had evidence of rheumatic heart disease. There was no correlation between the number and size of the nodules and the type or severity of the cardiac lesion, but it appeared that nodules were more frequent in children suffering from recurrent attacks of rheumatic fever. Nine of the twenty-eight patients died while under observation (33 per cent as compared to 16 per cent for the entire series). HECHT.

Lyons, R. H., Moe, G. K., Neligh, R. B., Hoobler, S. W., Campbell, K. N., Berry, R. L., and Rennick, B. R.: The Effects of Blockade of the Autonomic Ganglia in Man With Tetraethylammonium. Preliminary Observations on its Clinical Application. Am. J. M. Sc. **213**:315 (March), 1947.

Tetraethylammonium, a quaternary ammonium ion, was found by Acheson and Moe to block transmission of nerve impulses through autonomic ganglia in animals. This report concerns itself with the effects of such autonomic blockade in man and presents preliminary observations concerning its usefulness as a diagnostic and therapeutic agent in various disease states.

The drug was administered in doses of 0.2 to 0.5 Gm. intravenously, or up to 20 mg. per kilogram of body weight intramuscularly. The effects on the cardiovascular system were primarily the result of the release of vasoconstrictor tone; there was an increase in skin temperature, a transient fall in both systolic and diastolic pressure, postural hypotension, a fall in peripheral venous pressure, and an increase in heart rate and output. In two cases of acute myocardial infarction intravenous administration dramatically relieved the pain without the development of further changes in the electrocardiogram, despite a significant fall in blood pressure. The circulatory effects have been applied clinically in peripheral vasoconstrictor states, in relief of pain due to ischemia, in the relief of vasospasm, and as a diagnostic procedure. The effects in the gastrointestinal tract consisted of a cessation of normal peristalsis and a diminution in gastric secretion. This was applied clinically in the relief of pain and increased motility. Other effects included decrease in salivary secretion, cessation of sweating, incomplete dilatation of the pupil with loss of accommodation, decreased bladder tone, and abolishment of the urge to void. There was a significant relief of pain in causalgic states, which in a few instances failed to return after the immediate effects of the drug had disappeared. Toxic effects have been chiefly due to the ganglionic blocking action of the drug.

It is concluded that tetraethylammonium is a useful tool for the further study of disorders affecting the autonomic system, and that it is helpful in the selection of patients in whom surgery on the autonomic nervous system is to be considered. In selected cases the use of the drug may be of therapeutic as well as diagnostic value, especially in peripheral, vascular, and causalgic states. Though it will produce a transient fall in arterial pressure and has relieved symptoms of the complications of hypertension in a few instances, treatment of hypertension by repeated use of the drug does not appear feasible. DURANT.

Mayock, R. L., and Rose, E.: Insensitivity to Epinephrine in a Patient With a Functioning Tumor of the Adrenal Medulla. Am. J. M. Sc. **213**:324 (March), 1947.

A 42-year-old man had had attacks typical of paroxysmal hypertension for two and one-half years. At surgery a right-sided pheochromocytoma was removed which was found to contain 76.5 mg. of free epinephrine. Prior to surgery, doses of epinephrine up to 1.5 c.c. subcutaneously produced no rise in blood pressure. Following removal of the tumor there was a return of normal sensitivity to epinephrine. It is suggested that the demonstration of epinephrine insensitivity may serve as a useful and harmless test for the diagnosis of functioning tumors of the adrenal medulla. DURANT.

Cameron, D. E.: Increased Reactivity Caused by Adrenalin. Am. J. M. Sc. **213**:331 (March), 1947.

Administration of excessive amounts of adrenalin may result in severe head- and neckaches, in transitory blanching of the injected vein together with the appearance of goose primples, and in the persistence for several days of an increased pressor response to adrenalin. It seems reasonable to compare these findings with the situation which exists where the individual is exposed to repeated psychic traumata with repeated participation of the adrenosympathetic system, such as occurs in combat experience or in prolonged involvement in a guilt or other conflict situation. In these situations, as in those presented in the report, there frequently results an increased reactivity of those structures which react to the adrenosympathetic system. But these two situations differ in that the psychic traumata are repeated over long periods and lead, in a pro-

portion of cases, to such a degree of increased reactivity that response occurs to ordinary everyday stresses, resulting in the establishment of a self-perpetuating autonomous anxiety state.

DURANT.

Ruskin, A., and Decherd, G. M.: Thiamine Circulation Time. Am. J. M. Sc. **213**:337 (March), 1947.

Thiamine hydrochloride, in a standard supraoptimal dose of 300 mg., is a safe and exact subjective method for determining the speed of blood flow from arm to tongue. The normal circulation time by this method is 4 to 8 seconds in children and 5 to 13 seconds in adults. Studies have been made in 295 different cases, and values recorded for various grades of congestive heart failure and other disorders.

Circulation time, determined by any clinically used method, varies inversely with the dosage of the drug until a point is reached which may be called the true or shortest circulation time. This point is usually reached at a dose level of 200 to 300 mg. of thiamine, and may not be reached at the maximum safe dosage of 1 Gm. of magnesium sulfate, 0.48 Gm. of aminophylline, or 5 c.c. of 20 per cent decholin. Another source of error in doing circulation times with volumes of solution 5 c.c. or greater is the shortening apparently resulting from the rapid injection of these amounts under pressure. The thiamine method has the disadvantage of requiring the cooperation of the subject and the injection of rather large doses of the drug. It has the advantage of simplicity, safety, and exactness. In case of failure to respond to the 300 mg. dose, 600 mg., 900 mg., and even larger doses may be safely injected. To prevent another failure or delay in response, an interval of at least two hours between injections has been found satisfactory. Although no serious allergic or anaphylactic reactions have been encountered in more than a thousand injections, reports in the literature have emphasized the importance of a preliminary skin test, as well as the avoidance of an interval of one or two weeks between injections, as prophylactic measures.

DURANT.

Steiner, A., and Kendall, F. E.: Atherosclerosis and Arteriosclerosis in Dogs Following Ingestion of Cholesterol and Thiouracil. Arch. Path. **42**:433 (Oct.), 1946.

The authors discuss the inability to produce experimental cholesterol atherosclerosis in dogs comparable to that seen in rabbits. They state that hypercholesterolemia produced in dogs by high cholesterol (egg yolk) diets and by high fat diets will not give rise to atherosclerotic lesions. They, therefore, investigated cholesterol metabolism by altering thyroid function, knowing that marked hypercholesterolemia follows cholesterol feeding to thyroidectomized dogs. Surgical approach to the problem was difficult because of secondary malnutrition.

The authors, working with a group of four dogs, after control periods of two months of thiouracil alone, gave high cholesterol (in cottonseed oil) plus thiouracil up to 1.2 Gm. daily for fourteen months. The administration of thiouracil resulted in blood cholesterol elevations comparable to those obtained after thyroidectomy. The addition of high cholesterol diet in three of these dogs resulted in very high blood levels, and in one dog a higher level than any previously recorded.

Autopsy revealed typical atherosclerotic lesions in the aorta, the coronary, the thyroid arteries, and, to a lesser degree, in many other arteries. This was notable in the three dogs receiving the combined diet and thiouracil treatment. The fourth dog, which received thiouracil alone throughout the entire fourteen month period, showed thyroid enlargement similar to that in the other dogs, but did not have atherosclerosis. The authors point out the similarity of this type of atherosclerosis to that of human atherosclerosis in its location and morphologic character.

GOULEY.

West, H. F.: Heart Disease in the Case-Finding Program. Am. Rev. Tuberc. **54**:465 (Dec.), 1946.

Hundreds of x-ray films of the chest are being recorded daily throughout the nation and are accepted as the most accurate and rapid procedure for detecting early tuberculosis. Such roentgenograms obtained in mass surveys are being studied by various groups in order to deter-

mine their value in disclosing evidence of heart disease. These studies are of value in disclosing unsuspected cardiac enlargement due to hypertension or valvular lesion, pericardial disease, congenital anomalies, aortic arteriosclerosis, and other abnormalities.

For the past three years the Heart Division of the Los Angeles Tuberculosis and Health Association has participated in the case-finding project of the Industrial Health Program. From May, 1943, through February, 1946, a total of 63,398 persons have been x-rayed. In this series the interpretation of suspected tuberculosis was 2.7 per cent and of suspicious heart abnormalities, 2.0 per cent.

This author suggests that a joint committee, composed of members of the National Tuberculosis Association and the American Heart Association, be created to consider the value of this procedure, and if approved, to establish minimum standards or criteria for such surveys.

BELLET.

Burke, P. J.: Penicillin Prophylaxis in Acute Rheumatism. Lancet 7:25 (Feb. 15), 1947.

The author treated ten rheumatic patients prophylactically with penicillin by mouth for a year and compared the clinical findings with those in an untreated group of similar patients. Rheumatic manifestations were five times more frequent, and throat infections six times more frequent, in the untreated group than in the treated group. BELLET.

Braun, K., Roth, I., and Suesskind, S.: Intraventricular Block in Malnutrition and Vitamin B Deficiency. J. Pediat. 30:177 (Feb.), 1947.

The most commonly described electrocardiographic changes in vitamin B deficiency are depression and inversion of the T waves, prolongation of electrical systole, low voltage of the ventricular complexes, and premature beats. These changes have also been described in pellagra. The authors encountered two cases of malnutrition and vitamin B deficiency which showed intraventricular block. Both patients, a fifteen-month-old boy, and a five-year-old girl, showed widened QRS complexes. Both also showed T-wave changes. They were treated with liver extract, blood transfusions, vitamin B_1, and niacin. After nine and five days of treatment, respectively, both patients had normal electrocardiograms.

Reversible intraventricular block is rare and is encountered in acute heart failure, acute coronary insufficiency, acute infections, diphtheria, and digitalis overdosage. The question arises as to whether or not the changes in the myocardium are of metabolic origin, or whether they are organic in nature. The authors feel that the rapid electrocardiographic improvement observed in these patients suggests that the abnormalities were due to metabolic disturbances affecting the intraventricular conduction system. HAUB.

Erganian, J. A., Forbes, G., and Case, D.: Salicylate Intoxication in the Infant and Young Child. J. Pediat. 30:129 (Feb.), 1947.

Thirteen cases of salicylate intoxication were studied in infants and children ranging from 3 weeks to 3½ years of age. Laboratory determinations included plasma and spinal fluid salicylate concentration, pH of the blood serum, carbon dioxide content of the serum, prothrombin time, urine examination, and other procedures. The amount of salicylate ingested was determined in most instances by inquiry; this amount varied from 15 grains in two days to 126 grains in three days. Almost all the patients had received salicylates for either a cold or a cough. Clinically, they exhibited temperatures of from 38 to 40° C., were either pale or cyanotic, somewhat dehydrated, apathetic or stuporous, and showed some type of abnormal respiration. Other manifestations were: expistaxis, tarry stools, xanthochromia, twitchings, and convulsions. Plasma salicylate concentrations varied from 1.7 to 68.5 mg. per cent. In most of the cases, the amount of salicylate administered was greater than the limits of safety recommended by Mariott and Jeans (one grain per year of age every four hours). The carbon dioxide content of the serum was uniformly depressed and varied from 14 to 38 volumes per cent on admission. All patients received M/6 sodium r-lactate in Ringer's solution by the intravenous and subcutaneous route immediately on admission to the hospital and, in addition, were given parenteral vitamin K and vitamin C. Small whole blood transfusions were given to combat hemorrhagic tendencies. The patients

in severe acidosis were also in a state of circulatory collapse and were, therefore, also given oxygen. One patient died; permission for necropsy was not obtained.

The authors also studied the absorption curves of both acetyl salicylic acid and sodium salicylate in a group of children. The single dose absorption curves indicated that there probably would be a tendency toward accumulation of salicylate in the blood when administration was continued over a period of days. This assumption was borne out by further experiments.

In the absence of renal failure, diarrhea, diabetes, and other severe infections, the combination of hyperpnea, listlessness, and fever should suggest salicylate intoxication as a likely diagnosis. Because of the serious and progressive nature of such intoxication, emphasis is placed upon early diagnosis, frequent biochemical determinations, and prompt treatment. HAUB.

Poliakoff, H.: Mild Rheumatic Reaction in Coast Guard Recruits. Am. J. M. Sc. **213:** 37 (Jan.), 1947.

Each winter and spring a high incidence of acute ankle arthritis has been noted at the Coast Guard Training Station at Manhattan Beach. An analysis of the 1945 outbreak led to the conclusion that this is a mild manifestation of rheumatic fever. Of the fifty-two cases of rheumatic fever in the 1945 epidemic, 54 per cent ran a significantly similar course characterized by transient mild ankle arthritis with a paucity of other symptoms. Careful analysis of these mild cases showed definite rheumatic stigmata in thirteen (25 per cent). Of the twenty-nine cases in which electrocardiograms were taken, transient carditis was in evidence in five. The localization of the rheumatic fever manifestations to the ankles was attributed to local static and traumatic factors incident to recruit training. DURANT.

Chambers, W. N.: Blood Pressure Studies in 100 Cases of Coronary Occlusion With Myocardial Infarction. Am. J. M. Sc. **213:**40 (Jan.), 1947.

In an analysis of 100 cases of myocardial infarction it was found that the incidence of antecendent hypertension was greater (74 per cent) than in the general population. There was no relation between antecedent hypertension and the mortality rate in coronary occlusion, but in the hypertensive group the mortality was directly proportional to the degree of hypertension. Hypertension at the onset of the attack was a common finding (53 per cent) and occurred more frequently (68 per cent) in the fatal group. Hypotension in the initial reading was found in only 18 per cent. A fall in blood pressure occurred initially in 63 per cent, but all cases showed a fall at some time during the illness, although the fall often remained within hypertensive limits. An early return of the blood pressure to normal or preocclusion hypertensive levels was found to be a good prognostic sign. In the fatal group it usually did not return to its former level. The number of survivors who regained their original hypertension increased as the time elapsed after the occlusion, 58 per cent having regained their hypertension by the second year. After recovery from the initial coronary occlusion, the height of the blood pressure had no relationship to the frequency of recurrence or the ultimate prognosis. DURANT.

Gubner, R., DiPalma, J. R., and Moore, E.: Specific Dynamic Action as a Means of Augmenting Peripheral Blood Flow; Use of Aminoacetic Acid. Am J. M. Sc. **213:**46 (Jan.), 1947.

The effect on the peripheral blood flow of the ingestion of 20 Gm. of glycine dissolved in 200 to 300 c.c. of water or milk was investigated in twenty-five subjects, including nine patients with peripheral vascular disease. A rise in surface temperature was observed in the three regions tested; toes, fingers, and forehead. A significant increase in the temperature of the toes occurred in eleven normal subjects tested, and in three of four cases with peripheral vascular disease. The temperature of the fingers similarly increased in fourteen of fifteen cases. Forehead temperature increased in six of nine cases tested.

The temperatures attained, fully equivalent to the effect of posterior tibial nerve block in six cases in which comparison was made, indicate maximal vasodilatation. The effect exceeded that of alcohol in four cases in which the comparison was made between the ingestion of glycine and 2 ounces of whiskey. Oscillometric pulsation in the calf increased in eight of eleven normal sub-

jects, but no appreciable increase was observed in three cases with peripheral vascular disease. Blood flow to the extremities, as determined by venous occlusion plethysmography, was increased in eight of ten subjects examined, including four of five cases with peripheral vascular disease. The average increase was 62 per cent in the normal subjects and 30.5 per cent in those with peripheral vascular disease.

The increase in blood flow is an accompaniment of increased heat production (mainly in the liver) with attendant peripheral vasodilatation and increased cardiac output resulting from the specific dynamic action of glycine. The average maximal increase in oyxgen consumption above the basal level in eighteen cases studied was 18.4 per cent; the greatest individual rise was 52 per cent. The effect of glycine on oxygen consumption and on peripheral blood flow is manifest in one hour and is maximal after two to three hours. The specific dynamic action of glycine persists for a period of five to seven hours.

It is concluded that the ingestion of glycine provides a simple physiologic means of accomplishing an effective and sustained increase in peripheral blood flow. DURANT.

Friedman, N. B., Lange, K., and Weiner, D.: The Pathology of Experimental Frostbite. Am. J. M. Sc. **213**:61 (Jan.), 1947.

This study represents an attempt to correlate the morphologic aspects of the reactions of tissues to cold with modern physiologic concepts of the effects of low temperatures. It was found that the fundamental lesions of experimentally produced frostbite in rabbits are vascular. The formation of agglutinative erythrocytic thrombi lead to vascular occlusion and ischemic gangrene. While heparin did not prevent the early clumping of red cells within the vessels, it apparently did prevent the development of true agglutinative thrombi from the clumped erythrocytes by interfering in some way with the adhesiveness of the packed red cells; consequently, vascular lesions did not appear, and gangrene did not ensue. No changes in nerve or muscle attributable directly to cold were observed. DURANT.

Porter, W. B.: The Effect of Patent Ductus Arteriosus on Body Growth. Am. J. M. Sc. **213**:178 (Feb.), 1947.

This study concerns three patients with patent ductus arteriosus, aged 23, 34, and 11 years, respectively. Charts are presented comparing height, weight, and surface area with the other members of the family in the first two cases, and with a normal identical twin in the third. The charts show these patients to have been definitely influenced by some factor resulting in positive inhibition of body growth. The only apparent and consistent influence is that of patent ductus arteriosus which presumably resulted in a lessening of the normal supply of blood to the body tissues. A rapid increase in height was observed in the twin with patent ductus arteriosus following operative closure of the defect. The growth-inhibiting factor must therefore be considered an added reason for surgery, and the optimum time for operation is probably before the age of 11 years. DURANT.

Scherf, D., and Schlachman, M.: The Electrocardiographic Changes Caused by Hyperventilation. Am. J. M. Sc. **213**:342 (March), 1947.

The influence of hyperventilation on the electrocardiogram was studied. In a majority of the cases a lowering of the R and of the T waves in Lead I was noted. These changes were independent of the presence of an alkaline shift in the blood serum and independent of the signs and symptoms of tetany. The changes were identical, whether the hyperventilation consisted of rapid and shallow breathing, rapid and deep breathing, or slow and deep breathing. They appeared as early as three minutes after the beginning of hyperventilation and returned to normal within ten minutes after hyperventilation had ceased. The changes were the same as those which appeared when the electrocardiogram was taken during forced inspiration.

It is concluded that the alterations are explained by positional changes of the heart. As long as a marked increase in heart rate was avoided and the respirations were not sufficiently

rapid and shallow to cause anoxia, no depression of the RS-T segment was observed following hyperventilation. The alteration of the RS-T segments and the T-wave changes which may be observed in some women with endocrine imbalance is not due to hyperventilation. DURANT.

Thill, C. J., and Meyer, O. O.: Experiences With Penicillin and Dicumarol in the Treatment of Subacute Bacterial Endocarditis. Am. J. M. Sc. **213**:300 (March), 1947.

Of twenty-two patients with subacute bacterial endocarditis, thirteen received both penicillin and Dicumarol, and nine were given only penicillin. Despite the fact that the results were better in the group receiving combined therapy, the authors remain decidedly skeptical that anticoagulant therapy offers any advantages, and feel that it is unquestionable that anticoagulant therapy carries with it grave hazards in subacute bacterial endocarditis. Prolonged therapy, either with pencillin alone or combined with Dicumarol and persisting for a minimum of six weeks, gives decidedly better results than any other method. Sensitivity tests are of great value, since there is a good correlation between sensitivity and clinical response. It is of interest that five of the seven failures in this series occurred in patients who had received distinctly inadequate therapy before coming under observation, and this in spite of the fact that all but one of these had become subjectively and objectively improved under the original inadequate therapy. In one instance, it was found that penicillin given fourteen hours before and fifty-four hours after the extraction of a tooth, the dosage being 15,000 units every three hours, was inadequate to prevent the recurrence of subacute bacterial endocarditis in a patient whose disease had become arrested almost a year previously. DURANT.

Hodges, H. H., and Freeman, N. E.: Thrombophlebitis on the Medical Service of a General Hospital. Am. J. M. Sc. **213**:226 (Feb.), 1947.

This report is based on ten instances of thrombophlebitis in the lower extremity observed in a General Hospital during a four-month period. Eight of these developed in patients with scrub typhus fever (an incidence of 5 per cent in 130 consecutive cases). Treatment, the authors believe, should be individualized depending on the location and extent of the lesion. When thrombophlebitis is confined to the calf veins, lumbar paravertebral sympathetic block was used with uniformly good results. This procedure probably tends to prevent central propagation of the thrombus, embolism did not occur, and patients were spared the prolonged disability which follows femoral vein ligation. Anticoagulants might help prevent propagation of the thrombosis, but their use is usually unnecessary, and is prohibited in the presence of lumbar sympathetic block because of the danger of retroperitoneal hemorrhage. Thrombophlebitis involving the calf and femoral veins was treated by proximal ligation. Sympathetic block was used only for relief of pain after ligation. In one case of calf vein thrombosis with extension into the femoral vein, paravertebral procaine block prior to femoral ligation was followed promptly by pulmonary embolism. Iliofemoral thrombophlebitis was treated with heparin, high ligation being inadvisable in these ill patients. The results were satisfactory. In addition to the specific measures all patients were treated with elevation of the extremity, compression bandage, bed exercises, and early mobilization. From their observations the authors believe that all cases of iliofemoral thrombophlebitis do not necessarily result from extension of a calf vein thrombosis; such a process may originate occasionally in the iliofemoral region. DURANT.

King, B. G., and Henson, M.: Electrocardiographic Changes in Fulminating Anoxia. J. Aviation Med. **18**:3 (Feb.), 1947.

The authors investigated the rapidity with which electrocardiographic changes can occur in rapidly developing anoxia during altitude flights to obtain a better understanding of the mechanisms of rapidly deteriorating physiologic states, and to obtain information on the mechanisms underlying functional electrocardiographic changes. Special attention was given to the voltage and configuration of the P, QRS, and T deflections, S-T segment deviations, and durations of the P-R and Q-T intervals.

Anesthetized dogs were suddenly transferred from 100 per cent oxygen to 100 per cent helium or nitrogen. This procedure resulted in a most severe degree of anoxic anoxia which led to respiratory failure within 120 to 240 seconds. Cardiac failure occurred shortly thereafter, and resuscitative measures, applied four to five minutes after starting inhalation of the inert gas, failed in four of the nine cases in which remedial measures were attempted.

Records were taken from the first three standard leads during each minute of inhalation. The heart showed such marked changes in conduction, rhythm, or in origin of the beat, either before or shortly after the third minute of anoxia, that comparison of voltages, configurations, and intervals with control values was no longer warranted.

The most dramatic change during the period of co-ordinate activity was the increase in the potential of the T wave. The R wave decreased in voltage in two leads in seven of the eight dogs during exposure to helium and in seven of the eight during exposure to nitrogen. No significant or consistant change in the voltage of the P wave was observed. A high take off of the T wave was observed in five dogs breathing helium and in four dogs breathing nitrogen. Slowing of the heart after the initial acceleration occurred during the first minute in a majority of the dogs, although the acceleration stage was observed as late as the third minute in a few instances. The P-R intervals were all within the normal range as long as there was co-ordinate activity of the heart. Changes in QRS interval were within normal limits; such small changes as did occur being about equally divided between increased and decreased duration.

Human subjects breathing air were exposed for brief periods to simulated altitudes of 25,000 and 35,000 feet. In some instances, successive recordings of the first three standard leads were made during the development of anoxia. In others, progressive changes were followed in Lead II.

There was a consistant decrease in the voltage of the T wave in all of the eleven observations on seven subjects. Of the five subjects exposed to both altitudes, three showed the greater change at 35,000 feet and two at 25,000 feet. At the higher altitude changes were noted in ten seconds in four subjects, in thirty seconds in one subject, and in ninety seconds in one subject. Exposure to 25,000 feet resulted in changes in thirty to sixty seconds. At this altitude, transient increases in potential were noted in two cases after two and four minutes.

Changes in the R-wave potential were not consistent, but decrease in voltage occurred in four cases, with no change in five cases, and an initial increase of voltage with a return to the control value in two subjects. Small increases in the voltage of the P wave were seen in eight of the eleven trials. No significant changes in the P-R or the QRS intervals, or the S-T segment were noted.

The authors believe that the electrocardiographic changes which occur during brief exposure to anoxic anoxia are almost certainly attributable to functional changes and/or to shifts in the electrical axis of the heart rather than to permanent damage of the cardiac muscle. BELLET.

Dry, T. J., Butt, H. R., and Scheifley, C. H.: The Effect of Oral Administration of Para-Aminobenzoic Acid on the Concentration of Salicylates in the Blood: Preliminary Report. Proc. Staff. Meet., Mayo Clin. **21**:497 (Dec. 24), 1946.

The authors suggest that the action of salicylates in rheumatic fever may be more specific than has been recently supposed. It is known that rheumatic fever affects predominantly mesenchymal structures, the principal substrate of which is hyaluronic acid. The younger the tissue, the more readily will diffusion take place; and any agent capable of hydrolyzing hyaluronic acid increases this property.

The enzyme, hyaluronidase (derived from many strains of hemolytic types of streptococci and from extracts of umbilical cord and testes), is capable of just this action: it decreases the viscosity and favors the passage of liquids, exudates, and pathogenic tissues. When dyes are injected into the skin, the addition of hyaluronidase causes an increased diffusibility of these dyes, as demonstrated in both human beings and animals by Guerra. What is more impressive is that the extent of the spread is inhibited 57 to 66 per cent by the oral or intravenous administration of sodium salicylate, and that the degree of inhibition varies according to the dose of salicylate administered.

These observations are illuminating from the standpoint of the etiology and behavior of rheumatic fever when they are considered in the light of an enzyme system capable of producing

such profound and dramatic effects in special regions and tissues without actual direct bacterial invasion. Furthermore, the quantitative relationship which these reactions seem to bear to salicylate saturation cannot be without significance. If this is true, then the assurance of adequate quantities of salicylates in the blood must be of much importance, and may be directly related to those instances in which the therapeutic response is inadequate and in which relapses occur. It is in this connection that these authors introduced in this discussion the use of para-aminobenzoic acid.

The authors report a case in which they were unable to obtain a sufficiently high level of salicylates in the blood in spite of a liberal intake of salicylic acid, namely, 150 grains (10 Gm.), with an equal amount of sodium bicarbonate, per day. Following the simultaneous oral administration of para-aminobenzoic acid, in an initial dose of 4 Gm. followed by 2 Gm. every two hours around the clock, there resulted a steady increase in the salicylate level of the blood with a coincident dramatic clinical response.

In two control experiments involving healthy men these authors demonstrated that the content of salicylate in the blood obtained by a fixed daily dose of 10.6 Gm. of sodium salicylate with an equal amount of sodium bicarbonate increased considerably after the supplementary administration of para-aminobenzoic acid.

The authors conclude that salicylates and para-aminobenzoic acid appear to have a reciprocal effect in increasing their concentration in the blood when they are administered together orally. Additional studies are in progress to determine whether this phenomenon is dependent upon competitive excretion by the kidney or on some other metabolic effect. BELLET.

Kottke, F. J., Kubicek, W. G., and Laker, D. J.: Physical and Nervous Factors in Experimental Hypertension. Arch. Phys. Med. **28**:146 (March), 1947.

The authors studied the effect of diathermy on the systemic blood pressure, renal blood flow, and glomerular filtration of patients with hypertension. The patients were treated with diathermy for two hours daily for two to five weeks. In none of them was there an appreciable decrease of blood pressure. During each diathermy period there was a slight fall of blood pressure but no greater than would be found during a similar rest period. Six determinations of renal blood flow were carried out on four patients during diathermy treatment. Two determinations were made on a patient with severe hypertension during treatment with diathermy. This subject had an abnormally low renal plasma flow. In the first experiment, with a heat input of 104 calories per hour, there was no appreciable change in renal plasma flow during diathermy. The blood pressure rose slightly, and the pulse rate increased considerably. In the second experiment, with a heat input of 43 calories per hour, the renal plasma flow tended to fall throughout the diathermy treatment.

In other experiments, short wave diathermy was administered to the kidney region or to the head. In one of the experiments, on a 37-year-old man with a moderate hypertension, diathermy to the back resulted in a marked decrease of renal blood flow. The renal blood flow fell to 50 per cent of the initial value.

In this series of cases, diathermy decreased the renal blood flow in normotensive and hypertensive patients. The systemic circulatory reflexes responded to heat by increasing cutaneous circulation and decreasing renal as well as splanchnic blood flow. Since diathermy decreased renal blood flow, it appears to be of no value, or even harmful, in treating hypertension. BELLET.

Gertler, M. M., and Yohalem, S. B.: The Effect of Atabrine on Auricular Fibrillation and Supraventricular Tachycardia in Man. J. Mt. Sinai Hosp. **13**:323 (March-April), 1947.

This paper is presented as a preliminary report stressing the usefulness of atabrine in auricular fibrillation and paroxysmal supraventricular tachycardia as an alternative to quinidine.

The authors report a case of auricular fibrillation in a 55-year-old salesman who was admitted to the hospital with a temperature of 104.6 F., and a pulse of 80. No abnormalities were noted except for brawny, red, tender swelling of the left leg without cords, and the patient was treated for erysipelas of the leg. On the ninth day of hospitalization auricular fibrillation de-

veloped. Previous electrocardiograms had been abnormal. Two and half hours after the intramuscular administration of atabrine, there was a return of normal sinus rhythm.

The second case was an 88-year-old woman with nodal tachycardia who was admitted to the hospital in a semicomatose condition with a temperature of 100.6 F.; a pulse of 70; respirations, 30; and blood pressure 115/60. There were moist râles at the lung bases posteriorly, the heart was slightly enlarged, the heart sounds were well heard, and no murmurs or pathologic accentuations were present. Atabrine was administered intravenously and regular sinus rhythm was restored within forty-five seconds after the injection. The rhythm remained regular for two days at which time the patient died from the effects of diffuse carcinomatosis.

The authors feel that atabrine may have a distinct advantage over quinidine. In intramuscular doses of 0.4 Gm., atabrine reaches a blood level of 60 to 220 gamma per liter within one hour and falls to levels of 60 to 150 gamma per liter in three hours. The maximal effect, therefore, should occur early. Thus, in unselected cases of auricular fibrillation, one may know in three or four hours, instead of waiting five to ten as with quinidine, whether or not response is to be expected. In such instances, search for another drug such as digitalis may be begun earlier.

Atabrine should be used with caution unless one is completely familiar with its pharmacologic and physiologic properties, for the drug is not without toxicity. BELLET.

Kossberger, J.: Rheumatic Pneumonia. J. Pediat. **30**:113 (Feb.), 1947.

Evidence that rheumatic disease is the result of reaction to foreign antigens has been accumulating for a number of years. Infection with an organism such as the *Streptococcus hemolyticus* produces sensitivity rather than immunity of cells in other parts of the body. If further infection by the antigen occurs, an allergic reaction ensues. Foreign antigens may also cause the production of antibodies and if antigen and antibody meet in vascular tissue, the resulting reaction may injure the previously sensitized endothelial cell of the capillaries. It has been shown that an antigen consisting of streptococci and renal tissue can cause the formation of auto-antibodies, which react with the antigen in glomeruli to produce glomerulonephritis. It is possible that exudative lesions in rheumatic fever are produced by a similar response in cardiac tissue and other mesenchymal structures. Pulmonary lesions in rheumatic fever may be due to focal endothelial cell injury with increased capillary permeability, and transudation of albuminous fluid into the alveoli, alveolar ducts, alveolar septa, and interlobar spaces.

In addition, there is diapedesis of erythrocytes into alveoli, infiltration of the alveolar walls, and rupture of the walls with alveolar coalescence and intra-alveolar hemorrhage. The original albuminous transudate may be pressed against the alveolar wall by intra-alveolar air tension and become a hyaline membrane lining the alveoli and bronchioles. Septal cells, or possibly basal cells of bronchiolar epithelium, proliferate to form a single or stratified layer of cuboidal cells lining the alveoli. The plugs of fibrinous exudate which fill the alveolar ducts and project into the alveolar spaces become organized and form "Masson Bodies." These bodies are said to be present in bronchiectasis, tuberculosis, pulmonary abscess, and many other conditions.

Two cases of rheumatic pneumonitis are reported in detail. One was a girl 7 years of age, and the other a boy, aged 9 years. Both had active rheumatic infection, developed congestive failure, and both died three weeks after admission. Histologic examination of the lungs showed many of the characteristic features described above. HAUB.

Book Reviews

WHAT YOU CAN DO FOR ANGINA PECTORIS AND CORONARY OCCLUSION. By Peter J. Steincrohn, M.D., F.A.C.P., Doubleday and Company, Inc., Garden City, N. Y., 1946. Price $2.50. With 254 pages.

This is a sincere and highly successful attempt to talk to the patient in terms which cannot be misunderstood. With a few unimportant exceptions, the author's point of view can be heartily endorsed. Dr. Steincrohn is to be commended particularly for exploding several shabby old taboos. Most patients will profit from this book, and perhaps even enjoy it, but some will overlook the reassuring passages and become agitated by the fact that, after all, death is occasionally mentioned. Nothing but total insulation could ever protect such persons from emotional tailspins. It might be well, therefore, not to recommend this book indiscriminately to patients, but all physicians who deal with coronary artery disease should read it.

HORACE M. KORNS.

CARDIOPATOLOGIA. By A. A. Michelazzi. Rosenberg & Sellier, Torino, Italy, 1947. With 469 pages and 85 figures.

This book attempts to simplify Cardiology so that the practitioner may understand its basic principles, reach a diagnosis, and treat a patient without the help of a specialist.

While the description of methods of study is oversimplified, to the point that no mention is made of the precordial leads in electrocardiography, reference to these is made in the discussion of various diseases. The physiologic views of the author are not up to date, as is proven by the admission of a "cardiac tonus", by the statement that adrenalin is the sympathetic mediator, and by the claim that only one valvular event is responsible for each heart sound. The modern classification of gallop rhythms is ignored by the author; they are not clearly differentiated from the splitting of the heart sounds caused by bundle branch block. The statement that the "opening snap" of the mitral valve has no diagnostic importance should be questioned. The statement that peripheral edema is nearly constant and severe in adhesive pericarditis is contradicted by common observations.

Some inexactitudes are probably misprints: for example, the statement that the cyanosis of pulmonary stenosis is due to hypertension of the lesser circulation. The importance of blood pressure for the practitioner is not sufficiently emphasized; the factors responsible for and causing variations of this dynamic element are not properly stressed. The only phonocardiographic tracing reproduced in the book was apparently recorded with obsolete apparatus. Otherwise, phonocardiography is disregarded and many important interpretations in the field of clinical auscultation, demonstrated by this method, are omitted.

A curious fact should be noted: the doses of many digitalis preparations are given in grains. As the apothecary system is unknown in Italy, it is hard to understand how a practitioner in Italy will be able to evaluate them.

It is the reviewer's opinion that many discussions about the mechanism of various clinical disturbances could be omitted. The purpose of the book is sound. A new attempt in this direction should be encouraged because of the importance that such a work may have for the general practitioner.

A. LUISADA.

LA VELOCITA DELLA COZZENTE DEL SANGUE NELLA TERAPIA. By T. Sessa, L. Cappelli, Bologna, Italy, 1943. With 70 pages and 14 figures.

This monograph discusses circulation time and its importance in diagnosis and treatment. Many methods are described but the arm-to-lung test is omitted. After a brief study of the physiologic and clinical conditions causing variations of circulation speed, the author discusses the importance of these tests in general practice.

The following chapter deals with the actions of different drugs on circulation time. Digitalis and strophanthus glycosides, metrazol, caffeine, atropine, quinidine, ergotamine, pilocarpine, adrenaline, sympamine, sympathol, paredrinol, amyl nitrite, nicotinamide, thyroxine, insulin, histamine, mercurial diuretics, morphine, and heparin are discussed. The effects of bleeding, blood transfusion, paracentesis, pneumothorax, pneumoperitoneum, and anesthesia are also discussed. Drugs and physical procedures are then divided into two classes, those accelerating and those slowing the rate of circulation.

A less verbose discussion and a clearer understanding of both the factors of circulation and the actions of drugs would have increased the value of this booklet. Still, it may be useful as a reference manual since it contains a considerable amount of data.

A. LUISADA.

Correspondence

To the Editor:

In a paper in the January, 1947, issue of the American Heart Journal (vol. 33, pp. 1 to 13) on "Electrocardiographic Studies in Rheumatic Heart Disease," Doctors First, Stickle, and Bayley employ criteria for the electrocardiographic diagnosis of ventricular hypertrophy which are open to considerable question. The authors state: "The electrocardiogram shows a prominent R at V_5 and V_6 which indicates left ventricular hypertrophy." Furthermore, they say, "Fig. 5 shows a prominent S at V_2 and V_3 which indicates left ventricular hypertrophy." It is true that in the precordial electrocardiogram characteristic of left ventricular hypertrophy the R wave is usually abnormally large in leads from the left side of the precordium (V_5 and V_6) and the R wave is small or absent and followed by a deep negative deflection in leads from the right side of the precordium (V_1 and V_2). However, other abnormalities are often observed. Wilson and associates (Am. Heart J. **27**:19, 1944) have pointed out that the QRS interval is increased to .10 or .11 second and that the prominent R wave occurs abnormally late in the QRS interval in leads from the left side of the precordium (V_5 and V_6). This has been ascribed to the increased thickness of the left ventricular wall. In addition, both Wilson and associates and Goldberger (Am. Heart J. **28**:621, 1944) have described inverted T waves along with depression of the RS-T segment in these same leads when the precordial electrocardiogram was characteristic of left ventricular hypertrophy. Applying these criteria to the tracings which are claimed to demonstrate left ventricular hypertrophy in this paper, very few can be considered representative.

Further, the authors base their diagnosis of combined right and left ventricular hypertrophy on the findings of a prominent R and S in Leads V_2, V_3, and V_4 from the right side of the precordium and a prominent R at V_5 and V_6 from the left side of the precordium. These changes cannot be considered characteristic of combined ventricular hypertrophy. It is believed that the presence of the left ventricular hypertrophy when combined with right ventricular hypertrophy may produce changes in the long axis of the heart resulting in normal axis or even right axis deviation. However, the precordial electrocardiogram will resemble that seen in isolated left ventricular hypertrophy. (Goldberger, E.: Am. Heart J. **28**:621, 1944.) It is believed generally that it is difficult to determine the electrocardiographic presence of right ventricular hypertrophy when the precordial electrocardiogram is characteristic of left ventricular hypertrophy.

The questionable evidence of left ventricular hypertrophy presented in these electrocardiograms would seem to cast doubt upon the conclusion of these authors. "That left ventricular hypertrophy occurs more frequently as a result of rheumatic heart disease than does right ventricular hypertrophy," has not been proved convincingly by the data contained in this paper. It seems that a pathologic study of rheumatic heart disease with an attempt made to determine the ratio of the right and left ventricular weights would solve this problem better. Some of the other conclusions in this paper, based upon the electrocardiographic diagnosis of ventricular hypertrophy are open to question.

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The following is a reply to Dr. Schwartz' letter:

TO THE EDITOR:

The authors are aware of various points emphasized by Dr. Schwartz. He opens his communication with objection to the legend of Fig. 5. We feel that it is necessary to call his attention to Fig. 6 recorded from the same subject and to the fourth paragraph of the "Discussion" where we state, "Thus far, we have used the term hypertrophy when the R and S deflections in the precordial leads exceeded the standard offered by Wilson and associates.[9-12] It should be pointed out, however, that cardiac dilatation, which produces a closer proximity of the ventricular and the thoracic walls, may, by diminishing the distance from the exploring electrode to the accession wave, produce QRS deflections similar to those of hypertrophy. In subjects with electrocardiographic evidence of an initial increase in ventricular size and later a return to normal (Figs. 5 and 6), dilatation, rather than hypertrophy, probably predominates." Dr. Schwartz can have his choice.

With respect to the QRS interval: if Dr. Schwartz requires QRS intervals of .10 to .11 second for all curves on which he offers an electrocardiographic diagnosis of ventricular hypertrophy, there will be instances in which the latter will include intraventricular block; not to mention the fact that the majority of low-grade and moderate ventricular hypertrophies will be excluded arbitrarily, especially in children (with whom we were necessarily dealing).

With respect to the inverted T and deflection of the RS-T segment in subjects with left ventricular hypertrophy, these phenomena imply a more uniform duration (with respect to the normal) of the excited electrical state at the epicardial and the endocardial surfaces of the left ventricle, and it is true that this phenomena occurs relatively late in the course of hypertensive heart disease with pronounced hypertrophy of the left ventricle and often disappears quite rapidly following successful sympathectomy, but we fail to see its importance in connection with the present problem.

In an article entitled, "On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms Which Indicate Myocardial Disease" (Bayley, R. H.: AM. HEART J. **26**:769, 1943), the phenomena were described by stating that the free wall of the left ventricle acts electrically as if it were chronically ischemic. Again, if Dr. Schwartz requires this type of primary T-wave change to establish a diagnosis of left ventricular hypertrophy, he will lower unnecessarily the instance of his diagnosis of hypertrophy.

With respect to combined hypertrophy of the right and of the left ventricles, there is no sound reason why "right ventricular hypertrophy plus left ventricular hypertrophy should produce multiple precordial-lead effects which are identical to those of isolated left ventricular hypertrophy," and we do not agree that such is the case. We do agree, however, that the problem is occasionally difficult, particularly in single electrocardiograms. With combined hypertrophy of the right and left ventricles, the abnormally great amplitude of R and the delay of the chief downstroke in unipolar leads from the right side of the electrical precordium have the same significance with respect to the anticipated effects for isolated left ventricular hypertrophy as they have with respect to the normal. The same reasoning applies to dilatation in relation to the amplitude of R.

We would have no objection to a revision of our conclusions to include, "Left ventricular hypertrophy and/or dilatation occurs more frequently as a result of rheumatic heart disease than does right ventricular hypertrophy and/or dilatation." We are of the opinion that the unipolar precordial electrocardiogram offers the only accurate picture of ventricular size and is the only means whereby right ventricle enlargement can be differentiated from left. With the use of serial teleroentgenograms and fluoroscopy, we have frequently observed the development of an increase in the overall size of the cardiac silhouette when a diagnosis of low-grade or moderate ventricular hypertrophy was apparent in the electrocardiogram. In most instances, the increase in size of the cardiac silhouette was not of sufficient magnitude to alter the cardiothoracic ratio

from the normal, and it follows that the diagnosis of cardiac hypertrophy is unlikely in the majority of these teleroentgenograms. Our conclusions are also supported by a corresponding decrease in the size of the cardiac silhouette when the electrocardiogram shows a return to the normal (as was the case in Figs. 5 and 6).

Finally, we have every reason to believe that, if it were possible to obtain pathologic material on patients who have, as a rule, many years yet to live, this material would support our conclusions. In fact, in the occasional and all too frequent instances when death occurs relatively early in the overall course of rheumatic disease, primarily as the result of chronic rheumatic cardiac invalidism due primarily to recurrent active rheumatic myocarditis, the pathologic material obtained has supported our electrocardiographic findings. We are convinced that the general impression which our article contradicts was primarily due to the study of pathologic materials obtained at the end stage of prolonged rheumatic disease which leads most commonly to the "button hole" mitral stenosis and to secondary chronic pulmonary fibrosis and, only after the development of the latter, to chronic pulmonary arterial hypertension and right ventricular hypertrophy. We are not convinced that a ratio of ventricular weights is practical or sound. Even if it were practical, a ratio of ventricular weights might lend false support to our argument because of the greater fluid and substance of rheumatic inflammation in the left ventricular walls as compared to that in the right.

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Safety R. First, M.D

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